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IDENTIFICATION OF ENVIRONMENTAL CHEMICALS ASSOCIATED WITH THE DEVELOPMENT OF TOXICANT ASSOCIATED FATTY LIVER DISEASE IN RODENTS

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Abstract

Background—Toxicant associated fatty liver disease (TAFLD) is a recently identified form of non-alcoholic fatty liver disease (NAFLD) associated with exposure to industrial chemicals and environmental pollutants. Numerous studies have been conducted to test the association between industrial chemicals/ environmental pollutants and fatty liver disease both *in vivo* and *in vitro*.

Objectives—The objective of the paper is to report a list of chemicals associated with TAFLD.

Methods—Two federal databases of rodent toxicology studies– ToxRefDB (Environmental Protection Agency) and Chemical Effects in Biological Systems (CEBS, National Toxicology Program) were searched for liver endpoints. Combined, these two databases archive nearly 2000 rodent studies. TASH descriptors including fatty change, fatty necrosis, Oil red O positive staining, steatosis and lipid deposition were queried.

Results—Using these search terms, 123 chemicals associated with fatty liver were identified. Pesticides and solvents were the most frequently identified chemicals, while PCBs/dioxins were the most potent. About 44% of identified compounds were pesticides or their intermediates, and nearly 10% of pesticide registration studies in ToxRefDB were associated with fatty liver. Fungicides and herbicides were more frequently associated with fatty liver than insecticides.

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Conclusions—More research on pesticides, solvents, metals and PCBs/dioxins in NAFLD/TAFLD is warranted due to their association with liver damage.

Keywords

TASH; NAFLD; ToxRefDB; CEBS; pesticides; steatosis; steatohepatitis

Introduction

The liver is the first-line of defense against potentially harmful xenobiotics, and it is therefore the target organ that is most commonly affected by commercially-produced chemicals and environmental pollutants. Indeed, 33% of the 677 most common workplace chemicals reported in the National Institute of Occupational Safety and Health Pocket Guide are associated with hepatotoxicity (Tolman, 1998). The pathologic liver lesions associated with chemical exposures are myriad and range from hepatitis, fibrosis and cirrhosis to liver cancer (Cave, 2011). However, following the description of toxicant associated fatty liver disease (TAFLD) and its more severe form, toxicant associated steatohepatitis (TASH), it now appears that fatty liver may be the most common pathologic hepatic response to chemical exposure (Cave *et al.*, 2012, Wahlang *et al.*, 2013, Cave *et al.*, 2011b, Cave, 2011, Brautbar and Williams, 2002). Identifying TAFLD/TASH in humans is challenging for several reasons. The entity is clinically under-recognized; routine clinical biomarkers are insensitive; and out of the 88 million substances registered with the Chemical Abstracts Service (CAS) by 2014, there is no comprehensive list of chemicals correlated with TAFLD (CAS, 2014). As such, TAFLD is a clinicopathologic diagnosis which relies on histologic examination.

We have recently reviewed pathologic grading and staging systems and known molecular mechanisms of fatty liver disease (Wahlang *et al.*, 2013). The term “TASH” was initially coined in 2010 to describe steatohepatitis in human vinyl chloride workers (Cave *et al.*, 2010b). Liver biopsies from highly exposed workers resembled those from obese subjects (nonalcoholic steatohepatitis - NASH) or alcoholics (alcoholic hepatitis – ASH), although these workers were neither obese nor consumed alcohol. Relatively more is known about histologic abnormalities in NASH, and this is primarily driven by pharmaceutical clinical trials including the National Institutes of Health (NIH) sponsored NASH Clinical Research Network (Kleiner *et al.*, 2005). The NASH CRN uses, in part, histological improvement to determine the efficacy of experimental medications. Important pathologic lesions including steatosis, inflammation, and fibrosis have been included in these studies. Steatosis has been defined as an accumulation of triglycerides in at least 5% of hepatocytes (Aly and Kleiner, 2011; Canet *et al.*, 2012). The transition from steatosis to steatohepatitis is characterized by centrilobular (zone 3) centered injury and lobular inflammation (lymphocytes with neutrophils and activated Kupffer cells), hepatocyte ballooning and Mallory-Denk bodies and fibrosis (Kleiner and Brunt, 2012). While these findings are typically present on hemotoxylin and eosin (H&E), stained slides, other stains have been used such as Oil-Red-O which stains lipid droplets to quantify steatosis. Similar pathologic lesions have been observed in human TASH and in rodent models of steatohepatitis (Wahlang *et al.*, 2013).

TASH development may have similar mechanisms to other forms of fatty liver disease. TASH may be a progressive “two hit model” in which the “second hit” occurs on the background of steatosis and involves the elevation of inflammatory cytokines, mitochondrial dysfunction, insulin resistance, and oxidative stress which causes steatohepatitis and fibrosis (Day and James, 1998, Yilmaz, 2012). With time and persistence of exposure to these conditions, which can arise secondary to chemical exposure, steatohepatitis may progress to fibrosis and cirrhosis (Wahlang *et al.*, 2013, Cave *et al.*, 2010b, Cave *et al.*, 2011a).

Rodent models are widely utilized to study steatohepatitis. However these models typically do not recapitulate all aspects of the human diseased form (McGonigle and Ruggeri, 2014). In general, some rodent models tend to predominantly develop steatosis rather than inflammation and fibrosis (Bieghs and Shiri-Sverdlov, 2014). While many chemical exposure studies in rodents in the literature have reported the development of steatosis descriptors, the significance of these findings were not appreciated. This is because steatosis was erroneously believed to be a benign finding, at least prior to the description of NASH in 1980 (Ludwig *et al.*, 1980) and certainly TASH in 2010. The purpose of this study is to provide a list of chemicals that impact hepatic steatosis based on previously published rodent studies. A searchable archive of rodent studies provided in the websites of US Environmental Protection agency (EPA) and the National Institute of Environmental Health Sciences (NIEHS) presented a unique opportunity to accomplish this objective. The identification of environmental chemicals associated with the development of TAFLD will enable subsequent mechanistic animal studies and clinical translation in exposed humans.

Materials and Methods

Searchable databases

Two comprehensive chemical exposure and rodent pathology databases managed by the United States federal government were accessed for this study. The first was the EPA database known as **ToxRefDB** or the Toxicological Reference Database which was designed by the National Center for Computational Toxicology (NCCT) and the EPA Office of Pesticide Programs (OPP) which includes the past 30 years’ pesticide registration toxicity data and $2 billion of animal studies results (EPA, 2013). Using standardized vocabulary, ToxRefDB warehouses detail study design, dosing, and observed treatment-related effects. The ToxRefDB also stores chemical toxicity data in detail through freely accessible and searchable databases (EPA, 2013). ToxRefDB also connects with the ACToR (Aggregated Computational Toxicology Resource) in order to link it with public hazard, exposure and risk resources (EPA, 2013). Furthermore, ToxRefDB is connected to ToxCast, another EPA database and a high throughput screening tool that links exposure to biological processes affected by chemicals (EPA, 2013). ToxRefDB allows users to search congregate and group chemicals depending on the toxicological outcomes that are specific to the type of the study, target organ/effect categories (e.g., tumorigenicity) (Martin *et al.*, 2007). ToxRefDB classifies chemicals by their relative potency depending on specific endpoints/grouping of chemicals that also depends on the mechanism of action.

Currently, the ToxRefDB warehouses searchable pathologic information on 474 studies of pesticides and intermediates. In our study, the 474 rat/mouse studies were queried for

histological NAFLD and TASH descriptors including “fatty change”, “Oil red O positive”, “steatosis”, and “lipid deposition”. The data were accessed in Fall 2013 at http://actor.epa.gov/toxrefdb/faces/Home.jsp. The following study types were queried: sub-chronic (SUB), chronic (CHR) and multigeneration reproductive (MGR). MGR are studies performed in rodents to identify parental and offspring systemic toxicity and the reproductive toxicity of pesticides, industrial chemicals and pharmaceuticals (Martin *et al.*, 2009). The effect type selected was “pathology (non-neoplastic)”. The effect target was always the “liver” in the search and the effect descriptions were: “fatty change”, “lipid deposition”, “steatosis” and “Oil red O” positivity in increased effect direction (see supplemental material, ToxRefDB search instructions). Compounds selection was based on the altered NAFLD and TASH descriptors at the Lowest Effect Level (LEL). Compounds and their LELs were arranged and listed in tables.

The second rodent database utilized was the **Chemical Effects in Biological Systems (CEBS)** data repository developed by the National Toxicology Program (NTP) which warehouses about 9000 rodent toxicology studies (NTP). CEBS combines public toxicogenomics data including study design and timeline, clinical chemistry and histopathology, microarray and proteomics data (Waters *et al.*, 2008). CEBS warehouses data from academic, industrial and governmental laboratories, and it was mainly developed to allow public and free search though these data and studies (Sciences, 2012, Waters *et al.*, 2008). CEBS stores rats, mice and human subjects studies and it contains more than 4000 microarray hybridizations, and 75 2D gel images with protein identification (Waters *et al.*, 2008). Furthermore, CEBS comprises more than 1500 animals’ clinical chemistry and histopathology data (Waters *et al.*, 2008).

In Fall 2013, CEBS was accessed at: http://cebs.niehs.nih.gov. The queried assay domain was “histopathology” and the diagnoses selected were “fatty change” and “toxic hepatopathy” as the latter two terms appear to have been used to describe fatty liver in several National Toxicology Program (NTP) reports on polychlorinated biphenyls (PCBs) (National Toxicology, 2010). “Liver and all its parts” was always the target organ selected and all degrees of severity were included (see supplemental material, CEBS search instructions). The search initially returned 329 studies, but medications and natural products were subsequently manually excluded. Remaining compounds and their LELs were then arranged and listed in tables.

Results

ToxRefDB

At the Lowest Effect Level (LEL), 42 pesticides from 474 studies were associated with TAFLD pathologic descriptors including “fatty change”, “Oil red O positive”, “steatosis”, and “lipid deposition” (Tab. 1). The 42 compounds included 22 fungicides, 13 herbicides, 6 insecticides, and 1 miticide. These positive results came from both species (rat = 40 and mouse = 20) and from all queried study designs including sub-chronic (n = 16), chronic (n = 34) and multigeneration reproductive (n = 10). Thus nearly 10% of pesticide studies were associated with the development of TAFLD. Not all of these pesticides may be clinically relevant mediators of steatohepatitis due to the high LEL values reported in some cases.

However, 6 pesticides had LELs less than 10 mg/kg/day, and that increases the likelihood that they could be clinically significant mediators of TAFLD depending on their crop application patterns. These pesticides were: cyproconazole, dazomet, fluazinam, hexaconazole, pyrasulfotole metapolite (SXX 0665) and acequinocyl. Cyproconazole, dazomet, fluazinam, flusilazole, hexaconazole, paclobutrazol, triadimefon, vinclozolin and fluthiacet-methyl pesticides were associated with the development of steatosis in more than one study. This reproducibility increases the likelihood that exposures to these chemicals do indeed result in steatosis. Two fungicides, dazomet and hexaconazole, were linked to steatosis in 3 studies and had LELs <10 mg/kg/day in at least 2 studies. Supplemental Table 1 lists the 395 chemicals and their studied doses that did not produce histologic descriptors of fatty liver disease in rodents in the ToxRefDB database.

CEBS

Three hundred twenty nine studies of 81 chemicals reported positive TAFLD descriptors (“toxic hepatopathy” and “fatty change”). These chemicals included 31 solvents, plasticizers, monomers, and chemical intermediates (Tab. 2); 14 miscellaneous chemicals (Tab. 3); 12 pesticides and pesticide intermediates (Tab. 4); 9 fragrances, cosmetics and essential oils (Tab. 5); 9 paints, polishes, dyes and food additives (Tab. 6); and 6 PCBs and dioxin-like molecules (Tab. 7). Several chemicals from each class produced steatosis with LELs ≤ 10 mg/kg (7/14 pesticides; 6/6 PCBs and dioxin-like compounds; 4/31 solvents, plasticizers, monomers, and chemical intermediates; 3/9 paints, polishes, and dyes; 3/14 miscellaneous chemicals; and 1/9 fragrances; cosmetics, and essential oils). In CEBS, steatosis was reported in 29 mouse studies and 57 rat studies including both acute (n =9) and chronic (n =72) exposure models.

Discussion

Between CEBS and ToxRefDB, 371 studies linked 123 environmental chemicals to fatty liver disease in rodents. Pesticides composed almost 44% (54/123) of these chemicals and 14/55 pesticides produced steatosis with LELs less than 10. According to the US Environmental Protection Agency, a pesticide is: “any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest.” Though often misunderstood to refer only to insecticides, the term pesticide also applies to herbicides, fungicides, and various other substances used to control pests. Pesticides are a double-edged sword because they increase crop yields while simultaneously contaminating the food supply. The liver is responsible for the detoxification of these xenobiotic compounds primarily through cytochrome P450 enzymes; such as CYP3A and CYP2B families, that initiate the first step of the detoxification process (Nebert and Gonzalez, 1987, Nelson *et al.*, 1996). Thus, it is not surprising that the liver is a target organ for pesticide toxicity. Indeed many pesticides have previously been associated with fatty liver disease and aminotransferases elevation [reviewed in (Wahlang *et al.*, 2013)].

The present study increases the understanding of the role of pesticides in steatohepatitis. In particular, the potential roles of fungicides and herbicides in steatohepatitis appear to have been previously underestimated. Fungicides and herbicides are widely used for agricultural,

residential, and industrial purposes (Reigart, 2013). According to EPA, global annual fungicide application is nearly 500 million pounds (Reigart, 2013). Some azole antifungals including triadimefon, propiconazole and cyproconazole have been previously associated with hepatotoxicity and hepatomegaly in rats (Hester *et al.*, 2006, Peffer *et al.*, 2007). Interestingly, dazomet and hexaconazole were associated with fatty liver disease at relatively low LELs in multiple studies in ToxRefDB. Dazomet is a fungicide, herbicide and nematicide that in chronic mice studies produced hepatomegaly combined with large droplet steatosis (EPA, 2008, Authority, 1997). Hexaconazole is systemic triazole fungicide mainly used for the banana black and yellow sigatoka disease control (EPA, 1999). Hexaconazole was associated with hepatic enzyme elevation, hepatocellular hypertrophy, and hepatic fatty infiltration/changes in rodent and dog studies (EPA, 1999). Interestingly, in the present study, dazomet, hexaconazole, and 8 other pesticides in ToxRefDB were associated with steatosis descriptors in multi-generational reproductive studies. This may be the first evidence linking developmental pesticide exposures to fatty liver disease.

After pesticides, solvents were the class with the second highest number of chemicals (n=31) associated with steatosis in rodents. Solvents have been associated with hepatotoxicity since the late 1800s (Brautbar and Williams, 2002). Solvents are primarily used in industrial and military applications, but also have residential uses and contaminate the environment (Brautbar and Williams, 2002). Many solvents like vinyl chloride (VC) are halogenated hydrocarbons. Previous studies link exposure to VC and other haloalkanes/haloalkenes to steatohepatitis (Cave *et al.*, 2012). Furthermore, a Brazilian study on volatile petrochemical mixtures demonstrated that these chemicals caused NASH in exposed plant workers (Cotrim *et al.*, 1999). It is therefore not surprising than our study yielded 31 chemicals from this class, which has historically been the class most associated with steatohepatitis.

Paints, polishes and dyes have also previously been linked to liver disease. Abnormal serum transaminases have been reported in painters, but this may have been due to solvent co-exposures (Zimmerman, 1999, Dossing *et al.*, 1983). Likewise, liver enzyme elevation was reported in 44% of shoe repairmen (Tomei *et al.*, 1999). Moreover, Nigerian vat dye workers had increased serum transaminases levels (Soyinka *et al.*, 2007). Three of the chemicals associated with TAFLD in CEBS were azo dyes. Azo dyes are used as well to color textile, fabric, leather and papers. Exposure to azo food dyes including tartrazine and carmoisine resulted in aminotransferase elevation in a rodent study (Amin *et al.*, 2010). Four chemicals associated with TAFLD in this study are used for cosmetic purposes including hair coloring. Hair dyes have been proposed to influence the development of liver disease (Prince *et al.*, 2010). The potential role of food coloring additives and cosmetics in the development of NASH is intriguing due to their widespread use, and more data are needed.

Five PCBs/dioxins were associated with steatosis descriptors in this study; and all had very low LELs. PCBs are polychlorinated hydrocarbons that were commercially produced in the 1930s–1970s (Silberhorn *et al.*, 1990). PCBs are thermodynamically stable persistent organic pollutants, and thus PCB exposure remains relevant even though PCBs were banned in the 1970s. PCB exposures have been associated with suspected NALFD in epidemiological studies including the 2003–2004 adult National Health and Nutrition

Examination Survey (NHANES) (Cave *et al.*, 2010a). PCBs were also found to cause with hepatomegaly and slight increases in hepatic enzymes in workers in electrical capacitor factories in Taiwan (Yu *et al.*, 1997). We recently demonstrated that a non-dioxin-like PCB, PCB 153, worsened diet induced obesity and steatosis and was associated with hepatic antioxidant depletion (Wahlang *et al.*, 2011, Shi *et al.*, 2012). Likewise, dioxins have been associated with hepatic steatosis, in part due to increased lipid transport into hepatocytes (Lee *et al.*, 2010, Angrish *et al.*, 2013, Angrish *et al.*, 2012).

This study is not without several weaknesses, foremost of which are the pathologic descriptors used. While TAFLD is progressive disease characterized by steatosis, inflammation, and fibrosis, only steatosis descriptors were searched. “Steatohepatitis” is not a searchable term in either CEBS or ToxRefDB. Because inflammation/fibrosis queries could not be cross-matched with steatosis descriptors in CEBS/ToxRefDB, these terms were not included in the study as surrogates for steatohepatitis. This is because if hepatitis/fibrosis were present it would be unclear if the underlying disease was steatohepatitis or another other form of liver injury. Compounding the problem, precise terms for fatty liver disease such as steatosis were not available in some studies. Steatosis was not quantified and neither photomicrographs nor original publications were available on ToxRef/CEBS to allow for independent confirmation of the findings. Additionally, this study was solely dependent on pathologic descriptors and failed to address mode(s)-of-action. Potential human relevance, especially for compounds with high LEL’s is uncertain, and the effects of co-exposures (e.g. alcohol or high fat diet) were not addressed. Furthermore, only the lowest doses associated with fatty liver disease histologic descriptors are available at ToxRefDB. Determining chemicals not associated with fatty liver disease in CEBS was difficult due to the complexity of the database and lack of histologic descriptors for fatty liver disease in most of the chemicals studies.

Conclusions

From 371 studies archived in federal databases, 123 unique environmental chemicals were possibly linked to some form of fatty liver disease in rodents. Pesticides composed almost 44% of these chemicals. Thus, nearly 10% of pesticide registration toxicity studies reported the development of fatty liver disease. Some of these compounds were linked to liver disease at very low LELs, ≤ 10 mg/kg suggesting that these compounds could contribute to the development of steatohepatitis at environmentally relevant doses. Pesticides and solvents were the most frequently identified chemicals while PCBs/dioxins were the most potent (e.g. had the lowest LEL’s). Moreover, 395 chemicals were not associated with fatty liver disease at their studied doses in ToxRefDB. Given the high prevalence of both obesity and alcoholism, co-exposure to environmental chemicals, especially pesticides, may contribute to the development and progression of fatty liver disease. However, the effects of diet and alcohol on xenobiotic metabolism impacting TASH require further investigation. Therefore, these findings suggest that more research on the effects of pesticides, solvents, metals and PCBs/dioxins in steatohepatitis is required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

TASH	Toxicant Associated Steatohepatitis
NASH	Non-alcoholic Steatohepatitis
NAFLD	Non-alcoholic fatty liver disease
TAFLD	Toxicant associated fatty liver disease
ToxRefDB	Toxicological Reference Database
CEBS	Chemical Effects in Biological Systems
VC	Vinyl Chloride
PCBs	Polychlorinated biphenyls
NHANES	National Health and Nutrition Examination Survey
LEL	lowest effect dose
NIH	National Institutes of Health
CRN	Clinical Research Network
NTP	National Toxicology Program
EPA	Environmental Protection agency
CAS	Chemical Abstracts Service

References

EPA, United States Environmental Protection Agency. Computational Toxicology Research Program: ToxRefDB. 2013. http://www.epa.gov/ncct/toxrefdb/

Amin KA, Abdel Hameid H 2nd, Abd Elsttar AH. Effect of food azo dyes tartrazine and carmoisine on biochemical parameters related to renal, hepatic function and oxidative stress biomarkers in young male rats. Food Chem Toxicol. 2010; 48:2994–2999. [PubMed: 20678534]

Angrish MM, Dominici CY, Zacharewski TR. TCDD-elicited effects on liver, serum, and adipose lipid composition in C57BL/6 mice. Toxicological sciences : an official journal of the Society of Toxicology. 2013; 131:108–115. [PubMed: 22977169]

Angrish MM, Mets BD, Jones AD, Zacharewski TR. Dietary Fat Is a Lipid Source in 2,3,7,8-Tetrachlorodibenzo-rho-Dioxin (TCDD)-Elicited Hepatic Steatosis in C57BL/6 Mice. Toxicol Sci. 2012; 128:377–386. [PubMed: 22539624]

Authority, C.R.S.N.R. NRA Report on the Special Review of Metham Sodium, Dazomet and Methylisothiocyanate (MITC). Australia, C.O: 1997.

Bieghs, V.; Shiri-Sverdlov, R. Research on Diabetes I. 2014. Animal Models of Non-alcoholic Fatty Liver Disease: from Genetics to Nutrition.

Brautbar N, Williams J 2nd. Industrial solvents and liver toxicity: risk assessment, risk factors and mechanisms. Int J Hyg Environ Health. 2002; 205:479–491. [PubMed: 12455270]

CAS, C.A.S. CAS REGISTRY - The gold standard for chemical substance information. 2014. https://www.cas.org/content/chemical-substances

Cave M, Appana S, Patel M, Falkner KC, McClain CJ, Brock G. Polychlorinated biphenyls, lead, and mercury are associated with liver disease in American adults: NHANES 2003–2004. Environ Health Persp. 2010a; 118:1735–1742.

Cave M, Falkner KC, Henry L, Costello B, Gregory B, McClain CJ. Serum cytokeratin 18 and cytokine elevations suggest a high prevalence of occupational liver disease in highly exposed elastomer/polymer workers. J Occup Environ Med. 2011a; 53:1128–1133. [PubMed: 21915069]

Cave M, Falkner KC, Ray M, Joshi-Barve S, Brock G, Khan R, Bon Homme M, McClain CJ. Toxicant-associated steatohepatitis in vinyl chloride workers. Hepatology. 2010b; 51:474–481. [PubMed: 19902480]

Cave, M.; Falkner, KC.; McClain. A Textbook of Liver Disease (Hepatology). Elsevier Saunders; Philadelphia, PA: 2011. Occupational and Environmental Hepatotoxicity; p. 476-492.

Cave MC, Beier JI, Wheeler B, Falkner KC, Bellis-Jones HJ, Clair HB, McClain CJ. Occupational Vinyl Chloride Exposures Are Associated With Significant Changes To The Plasma Metabolome: Implications For Toxicant Associated Steatohepatitis. Hepatology. 2012; 56:882A–883A.

Cave MC, Falkner KC, Costello B, McClain CJ. Serum Cytokeratin 18 and Cytokine Elevations Suggest a High Prevalence of Occupational Liver Disease in Elastomer/Polymer Workers Highly Exposed to Acrylonitrile, Butadiene and Styrene. Gastroenterology. 2011b; 140:S975–S975.

Cotrim HP, Andrade ZA, Parana R, Portugal M, Lyra LG, Freitas LA. Nonalcoholic steatohepatitis: a toxic liver disease in industrial workers. Liver. 1999; 19:299–304. [PubMed: 10459628]

Day CP, James OF. Steatohepatitis: a tale of two “hits”? Gastroenterology. 1998; 114:842–845. [PubMed: 9547102]

Dossing M, Arlien-Soborg P, Milling Petersen L, Ranek L. Liver damage associated with occupational exposure to organic solvents in house painters. Eur J Clin Invest. 1983; 13:151–157. [PubMed: 6409638]

EPA, United States Environmental Protection Agency. RED Fact Sheet: Dazomet. 2008.

EPA, United States Environmental Protection Agency. Hexaconazole (ANVIL 25 SC; ANVIL 25EC/OL» in or on Imported Bananas. 1999.

Hester SD, Wolf DC, Nesnow S, Thai SF. Transcriptional profiles in liver from rats treated with tumorigenic and non-tumorigenic triazole conazole fungicides: Propiconazole, triadimefon, and myclobutanil. Toxicol Pathol. 2006; 34:879–894. [PubMed: 17178689]

Kleiner DE, Brunt EM. Nonalcoholic fatty liver disease: pathologic patterns and biopsy evaluation in clinical research. Semin Liver Dis. 2012; 32:3–13. [PubMed: 22418883]

Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, Liu YC, Torbenson MS, Unalp-Arida A, Yeh M, McCullough AJ, Sanyal AJ. Nonalcoholic Steatohepatitis Clinical Research, N. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005; 41:1313–1321. [PubMed: 15915461]

Lee JH, Wada T, Febbraio M, He J, Matsubara T, Lee MJ, Gonzalez FJ, Xie W. A novel role for the dioxin receptor in fatty acid metabolism and hepatic steatosis. Gastroenterology. 2010; 139:653–663. [PubMed: 20303349]

Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc. 1980; 55:434–438. [PubMed: 7382552]

Martin, MT.; Judson, R.; Richard, AM.; Houck, KA.; Dix, DJ. ToxRefDB: Linking regulatory toxicology information on environmental chemicals with high-throughput screening (HTS) and genomic data. International Science Forum on Computational Toxicology; RTP, NC. May 21–23; 2007.

Martin MT, Mendez E, Corum DG, Judson RS, Kavlock RJ, Rotroff DM, Dix DJ. Profiling the reproductive toxicity of chemicals from multigeneration studies in the toxicity reference database. Toxicological sciences : an official journal of the Society of Toxicology. 2009; 110:181–190. [PubMed: 19363143]

McGonigle P, Ruggeri B. Animal models of human disease: challenges in enabling translation. Biochem Pharmacol. 2014; 87:162–171. [PubMed: 23954708]

National Toxicology, P. Toxicology and carcinogenesis studies of 2,3′,4,4′,5-pentachlorobiphenyl (PCB 118) (CAS No. 31508-00-6) in female harlan Sprague-Dawley rats (gavage studies). Natl Toxicol Program Tech Rep Ser. 2010:1–174.

Nebert DW, Gonzalez FJ. P450 genes: structure, evolution, and regulation. Annual review of biochemistry. 1987; 56:945–993.

Nelson DR, Koymans L, Kamataki T, Stegeman JJ, Feyereisen R, Waxman DJ, Waterman MR, Gotoh O, Coon MJ, Estabrook RW, Gunsalus IC, Nebert DW. P450 superfamily: update on new sequences, gene mapping, accession numbers and nomenclature. Pharmacogenetics. 1996; 6:1–42. [PubMed: 8845856]

NTP. New CEBS File Assists Database Collaboration. http://ntp.niehs.nih.gov/?objectid=29376036-D423-4AC0-55E9F014611F94B3

Peffer RC, Moggs JG, Pastoor T, Currie RA, Wright J, Milburn G, Waechter F, Rusyn I. Mouse liver effects of cyproconazole, a triazole fungicide: role of the constitutive androstane receptor. Toxicological sciences : an official journal of the Society of Toxicology. 2007; 99:315–325. [PubMed: 17557908]

Prince MI, Ducker SJ, James OF. Case-control studies of risk factors for primary biliary cirrhosis in two United Kingdom populations. Gut. 2010; 59:508–512. [PubMed: 20332522]

Reigart, JRRaJR. Recognition and management of pesticide poisonings. The National Association of State Departments of Agriculture Research Foundation (NASDARF); 2013. Fungicides; p. 143-116.

Sciences, N.I.O.H. Chemical Effects in Biological Systems (CEBS). 2012. http://www.niehs.nih.gov/research/resources/databases/cebs/

Shi X, Wahlang B, Wei X, Yin X, Falkner KC, Prough RA, Kim SH, Mueller EG, McClain CJ, Cave M, Zhang X. Metabolomic analysis of the effects of polychlorinated biphenyls in nonalcoholic fatty liver disease. J Proteome Res. 2012; 11:3805–3815. [PubMed: 22686559]

Silberhorn EM, Glauert HP, Robertson LW. Carcinogenicity of polyhalogenated biphenyls: PCBs and PBBs. Critical reviews in toxicology. 1990; 20:440–496. [PubMed: 2165409]

Soyinka OO, Adeniyi FA, Ajose OA. Biochemical parameters of liver function in artisans occupationally exposed to “vat dyes”. Indian J Occup Environ Med. 2007; 11:76–79. [PubMed: 21938220]

Tolman KG, Sirrine R. Occupational hepatotoxicity. Clin Liver Dis. 1998:563–589.

Tomei F, Giuntoli P, Biagi M, Baccolo TP, Tomao E, Rosati MV. Liver damage among shoe repairers. Am J Ind Med. 1999; 36:541–547. [PubMed: 10506736]

Wahlang B, Beier JI, Clair HB, Bellis-Jones HJ, Falkner KC, McClain CJ, Cave MC. Toxicant-associated steatohepatitis. Toxicol Pathol. 2013; 41:343–360. [PubMed: 23262638]

Wahlang B, Zhang X, Falkner KC, McClain CJ, Cave MC. Polychlorinated Biphenyl 153 Worsens Hepatic Steatosis in Mice Fed a High Fat Diet and Differentially Regulates 40 Liver Metabolites: Preliminary Results of a Metabolomics Analysis. Hepatology. 2011; 54:1156A–1156A.

Waters M, Stasiewicz S, Merrick BA, Tomer K, Bushel P, Paules R, Stegman N, Nehls G, Yost KJ, Johnson CH, Gustafson SF, Xirasagar S, Xiao N, Huang CC, Boyer P, Chan DD, Pan Q, Gong H, Taylor J, Choi D, Rashid A, Ahmed A, Howle R, Selkirk J, Tennant R, Fostel J. CEBS--Chemical Effects in Biological Systems: a public data repository integrating study design and toxicity data with microarray and proteomics data. Nucleic Acids Res. 2008; 36:D892–900. [PubMed: 17962311]

Yilmaz Y. Review article: is non-alcoholic fatty liver disease a spectrum, or are steatosis and non-alcoholic steatohepatitis distinct conditions? Aliment Pharmacol Ther. 2012; 36:815–823. [PubMed: 22966992]

Yu ML, Guo YL, Hsu CC, Rogan WJ. Increased mortality from chronic liver disease and cirrhosis 13 years after the Taiwan “yucheng” (“oil disease”) incident. Am J Ind Med. 1997; 31:172–175. [PubMed: 9028433]

Zimmerman, HJ. Hepatotoxicity : the adverse effects of drugs and other chemicals on the liver. Lippincott Williams & Wilkins; Philadelphia: 1999.

Table 1

Pesticides associated with fatty liver disease in ToxRefDB.

	Chemical Name	Study Design and species	Administration route	MIRD*	LDT (mg/kg/day)	HDT (mg/kg/day)	LEL (mg/kg/day)	Citation
Fungicides:								
1.	Bromuconazole	Mouse-Subchronic	Oral	42937131	2.72	381	68.1	Broadmeadow, A. (1990) LS860263: Toxicity Study by Dietary Administration to F-344 Rats for 13-Weeks: Final Report: Lab Project Number: RHA/192/860263: 88/RHA192/0888: 88/0888. Unpublished study prepared by Life Science Research Ltd. 323 p.
2.	Cyproconazole	Rat-Chronic	Oral	41164701	1.01	21.8	15.6	Warren, S.; Carpy, S.; Muller, F. (1988) SAN 619 F: Chronic Toxicity/Oncogenicity Feeding Study in Rats: Project No. 357-R; Report No. CBK I. 6858/87. Unpublished study prepared by Sandoz Ltd. 2225 p.
		Rat-MGR**	Oral	40607723	0.28	13.3	8.29	Eschbach, B.; Aerni, R.; Karapally, J.; et al. (1987) SAN 619F: 2-Generation Reproduction Study in Rats: Project No. 380-R; Report No. 6712/87. Unpublished study prepared by Sandoz, Ltd. 592 p.
3.	Dazomet	Rat-Chronic	Oral	41865001	0.2	4.83	3.71	Kuhbroth, B. (1989) Report On The Oncogenic Potential Of Dazomet in Rats After 24 Month Administration in The Diet: Lab Project Number: 89/0277. Unpublished Study Prepared By Basf Aktiengeselschaft 1321 P.
		Mouse-Chronic	Oral	41865101	3.9	95	69.9	Kunbroth, B. (1989) Report On The Study Of The Oral Toxicity Of Dazomet Mice After 78 Week Administration in The Diet: Lab Project Number: 89/0341. Unpublished Study Prepared By Basf Ag. 10 P.
		Rat-MGR*	Oral	41865301	0.46	19	2.78	Hellwig, J. (1989) Report On The Reproduction Study With Dazomet in Rats; Continuous Dietary Administration Over 2 Generations (2 Litters in The First And 1 Litter in The Second Generation): Lab Project Number: 89/0051. Unpublished study prepared by Basf AG
4.	Diethyl 4,4′-o-phenylenebis (3-thioallophanate)	Mouse-Chronic	Oral	32674	0.48	300	300	Hashimoto, Y. and Tsubura, Y. (1972) Final Report on the Chronic Oral toxicity studies of thiophanate-methyl, Dimethyl 4, 4′-O-phenylenebis(3-thioallophanate) in rats of Sprague-Dawley Strain for 24 months. Unpublished report from Nisso Institute for Life Sciences, Nippon Soda Co. Ltd.
5.	Difenoconazole	Mouse-Chronic	Oral	42090015	1.51	819	819	Cox, R. (1989) CGA-169374 Technical: Oncogenicity Study in Mice: Final Report: Lab

	Chemical Name	Study Design and species	Administration route	MIRD*	LDT (mg/kg/day)	HDT (mg/kg/day)	LEL (mg/kg/day)	Citation
								Project Number: 483-250. Unpublished study prepared by Hazleton Labo Project Number: 483-250. Unpublished study prepared by Hazleton Labo Project Number: 483-250. Unpublished study prepared by Hazleton Labo
6.	Dimethomorph	Rat-Subchronic	Oral	42233910	2.9	82	14.2	Ruckman, S.; Crook, D.; Gopinath, C.; et al. (1987) Toxicity to Rats by Dietary Admixture for 13 Weeks with a 4-Week Withdrawal Period: Lab Project Number: CMK 7/8624. Unpublished study prepared by Huntingdon Research Centre Ltd. 259 p.
7.	Famoxadone	Mouse-Chronic	Oral	44302424	0.701	392	274	Mackenzie, S. (1996) Oncogenicity Study With Dpx-Je874-221: Eighteen-Month Feeding Study in Mice: Lab Project Number: 526-95: Hlr 526-95: 9734-001. Unpublished Study Prepared By Haskell Lab. For Toxicology And Industrial Medicine. 1643 P.
8.	Fenarimol	Rat-Chronic	Oral	45502305	2	21.6	14.6	Hoffman, D.; Gibson, W.; Pierce, E. et al. (1978) Twenty-Four Month Chronic Oral Toxicity of EL-222 (56722) in Rats Studies R-405 and R-415: Lab Project Number: 33428: 235173A. Unpublished study prepared by Lilly Research Laboratories. 399 p.
		Mouse-Chronic	Oral	71920	7	86	86	Hoffman, D.G.; Pierce, E.C.; Emmerson, J.L.; et al. (1978) Twenty-four Month Chronic Oral Toxicity of EL-222 (56722) in Mice: Studies M-9135 and M-9145. (Unpublished study received Sep 22, 1978 under 1471-EX-50; submitted by Elanco Products Co., Div. of Eli. Lilly & Co.
9.	Fluazinam	Rat-Chronic	Oral	42248620	0.04	53.0	40	Mayfield, R.; Burton, S.; Crook, D.; Et Al. (1988) Fluazinam Technical (B1216): Potential Carginogenicity And Chronic Toxicity Study in Dietary Administration To Rats For 104 Weeks: Lab Project Number: Isk 8/87263. Unpublished Study Prepared By Huntingdon
		Rat-MGR*	Oral	42248619	1.5	53.6	9.7	Tesh, J.; Willoughby, C.; Fowler, J. (1987) Fluazinam Technical (B1216): Effects Upon Reproductive Performance Of Rats Treated Continuously Throughout Two Successive Generations: Lab Project Number: 87/Isk068/097. Unpublished Study Prepared By Life Sciences Research
10.	Flusilazole	Rat-Subchronic	Oral	0	2	70	55	Pastoor et al. (1983) 90-day oral feeding study in rats. Haskell Labs sponsored by E.I. du Pont de Nemours and Co.
		Rat-Chronic	Oral	40042112	0.4	13	13	Pastoor, T. (1986) Long-term Feeding and Two-generation, Four-litter Reproduction Study in Rats

	Chemical Name	Study Design and species	Administration route	MIRD*	LDT (mg/kg/day)	HDT (mg/kg/day)	LEL (mg/kg/day)	Citation
								with in H-6573: Haskell Laboratory Report No. 32-86 with in H-6573: Haskell Laboratory Report No. 32-86
11.	Hexaconazole	Rat-Subchronic	Oral	40944805	2.5	250	25	Kinsey, D.; Hollis, K.; Chart, I.; et al. (1984) PP 523: 90-day Feeding Study in Rats including Individual Animal Data Supplement: Laboratory Project ID: CTL/P/1073 & CTL/P/1073S. Unpublished study prepared by Central Toxicology Laboratory, ICI America
		Rat-Chronic	Oral	40944808	0.47	61	4.7	Hext, P. (1988) Hexaconazole: Two Year Feeding Study in Rats including Individual Animal Data Supplement: Laboratory Project ID: CTL/P/1920. Unpublished study prepared by ICI Central Toxicology Laboratory, ICI Americas Inc. 2776 p.
		Rat-MGR*	Oral	40944813	1.0	50	5	Middleton, M. (1988) Hexaconazole: Two-generation Reproduction Study in the Rat including Individual Animal Data Supplement: Laboratory Project ID: CTL/P/1598. Unpublished study prepared by ICI Central Toxicology Laboratory. 1717 p.
12.	Iprodione	Mouse-Chronic	Oral	42825002	23	793	604	Chambers, P.; Crook, D.; Gibson, W.; et al. (1993) Iprodione: Potential Tumorigenic Effects in Prolonged Dietary Administration to Mice: Lab Project Number: RNP 359/921240. Unpublished study prepared by Rhone-Poulenc Agrochimie, Huntingdon Research Centre
13.	Propiconazole	Rat-Chronic	Oral	129918	3.6	101	96.4	Hunter, B.; Slater, N.; Heywood, R.; et al. (1982) CGA 64 250: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats: CBG 193/8284 (Test No. 789023). Final rept. (Unpublished study received Jul 21, 1983 under 100-641
14.	Metalaxyl	Rat-MGR*	Oral	71600	2.5	62.5	62.5	Cozens, D.D.; Allen, P.A.; Clark, R.; et al. (1980) Effect of CGA 48-988 on Reproductive Function of Multiple Generations in the Rat: CBG 181/80254. (Unpublished study received Apr 15, 1981 under 100-607; prepared by Huntingdon Research Centre, England,
15.	Oxytetracycline hydrochloride	Rat-Chronic	Oral	159856	1250	2500	1250	Us Public Health Service (1986) Toxicology And Carcinogenesis Studies Of Oxytetracycline Hydrochloride (Cas No. 2058-46-0) in F344/N Rats And B6C3F1 Mice: (Feed Studies): Technical Report Series No. 315: [NIH Publication No. 86-2571]: Draft. Unpublished
16.	Paclobutrazol	Mouse-Chronic	Oral	40762501	3.75	113	113	Shaw, D. (1986) Paclobutrazol: 104 Week Oral (Dietary Administration) Combined Toxicity and Carcinogenicity Study in the Mouse with a 52

	Chemical Name	Study Design and species	Administration route	MIRD*	LDT (mg/kg/day)	HDT (mg/kg/day)	LEL (mg/kg/day)	Citation
								Week Interim Kill: Laboratory Project ID: CTL/C/1759A, [illegible], C and E. Ur Week Interim Kill: Laboratory Project ID: CTL/C/1759A, [illegible], C and E. Ur Week Interim Kill: Laboratory Project ID: CTL/C/1759A, [illegible], C and E. Ur
		Rat-MGR*	Oral	40734303	2.5	62.5	62.5	Wickramaratne, G. (1987) Paclobutrazol: Two Generation Reproduction Study in Rats including Individual Animal Data: Laboratory Project ID: CTL/P/1496 and CTL/P/1496S. Unpublished study prepared by ICI Central Toxicology Laboratory. 1953 p.
17.	Propanoic acid, 2-(2,4-dichlorophenoxy)-, (R)-	Rat-Subchronic	Oral	43915101	7	245	144	Mellert, W.; Deckardt, K.; Kaufmann, W.; et al. (1995) Dichlorprop-P--Subchronic Oral Dietary Toxicity and Neurotoxicity Study in Wistar Rats: Lab Project Number: 50C0187/91158: 92/32/EEC. Unpublished study prepared by BASF AG 653 p.
18.	Triadimefon	Rat-Chronic	Oral	42153901	2.7	199	114	Bomhard, E.; Schilde, B. (1991) MEB 6447: Chronic Toxicity and Cancerogenicity Studies on Wistar Rats with Administration in Diet over a Period of 105 Weeks: Lab Project Number: 20774: 101922. Unpublished study prepared by Bayer Ag., Dept. of Toxicology.
		Mouse-Chronic	Oral	40752101	13.5	765	550	Bomhard, E. (1986) MEB 6447: Carcinogenicity Study on NMRI Mice (21-Month Administration in the Feed): Report No. 87287. Unpublished study prepared by Bayer AG. 1190 p.
19.	Triadimenol	Rat-Subchronic	Oral	42192701	8	221	39.6	Nishimura, N. (1983) Subacute Toxicity Study of KWG 0519 in Dietary Administration to Rats for 13 Weeks: Lab Project Number: 101939. Unpublished study prepared by Bozo Research Center Inc. 320 p.
20.	Trifloxystrobin	Mouse-Chronic	Oral	44496705	3.51	274	274	Gerspach, R. (1997) 18-Month Carcinogenicity Study in Mice: Cga-279202 Tech: Lab Project Number: 943039: 705-97. Unpublished Study Prepared By Novartis Crop Protection, Ag. 1802 P.
21.	Triflumizole	Mouse-Chronic	Oral	156544	16.2	362	67.4	Inoue, H. (1984) Chronic Feeding And Oncogenicity Studies in Mice With Nf-114: Rd-84114: Experiment No. 098 (026-001). Unpublished Study Prepared By Nippon Soda Co., Ltd. 2565 P.
22.	Vinclozolin	Mouse-Chronic	Oral	43254704	2.1	1410	1230	Mellert, W. (1994) Toxicology Study Report: Carcinogenicity Study with Reg. No. 83 258: Vinclozolin in C57BL Mice Administration in the Diet for 18 Months: Lab Project Number: 80S0375/88112: 94/10278. Unpublished study prepared by BASF AG

	Chemical Name	Study Design and species	Administration route	MIRD*	LDT (mg/kg/day)	HDT (mg/kg/day)	LEL (mg/kg/day)	Citation
		Rat-MGR*	Oral	42581301	4.9	290	290	Hellwig, J. (1992) Report Reproduction Study with Reg. No. 83 258 (Vinclozolin) in Rats Continuous Dietary Administration over 2 Generations (2 Litters in the First and 2 Litters in the Second Generation): Lab Project Number: 92/11251: 71R0375/88053. Unpubl.
23.	Bensulide	Rat-Subchronic	Oral	43919601	5	100	100	Mulhern, M.; Hudson, P.; Snodgrass, E. (1992) Bensulide: 13 Week Subchronic Dietary Toxicity Study in Rats: Lab Project Number: 7948: 451068. Unpublished study prepared by Inveresk Research Int'l. 236 p.
24.	Butafenacil	Rat-Chronic	Oral	45426401	0.39	13	13	Gespach, R. (1998) 24-Months Carcinogenicity And Chronic Toxicity Study in Rats: Cga-276854 Technical: Final Report: Lab Project Number: 951029: 851-95. Unpublished Study Prepared By Novartis Crop Protection, Inc. 2431 P. {Oppts 870.4300}
25.	Chlorsulfuron	Rat Chronic	Oral	40089316	2	405	309	Stula, E. (1985) Two-year Rat Feeding Study and Two-generation Reproduction Study: Report No. HLR-662-85. Unpublished study prepared by Haskell Laboratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours & Co., Inc. 1712p.
26.	Ethofumesate	Rat-Subchronic	Oral	44093601	18.2	2310	1900	Powell, L.; Copeland, A.; Copinath, C. et al. (1989) T510 Ethofumesate: Toxicity to Rats by Dietary Administration for 13 Weeks (According to OECD Guidelines): (Final Report): Lab Project Number: A89580: RKY 86/881321: RKY/86. Unpublished study prepared
27.	Fluthiacet-methyl	Rat-Subchronic	Oral	43348423	0.6	1420	216	Potrepka, R.; Morrissey, R. (1993) 90-Day Dietary Toxicity Study with CGA-248757 Technical in Rats: Final Report: Lab Project Number: F-00066. Unpublished study prepared by CIba-Geigy Environmental Health Center. 572 p.
		Rat-Chronic	Oral	43830017	0.2	368	130	Potrepka, R.; Richter, A. (1995) Two-Year Dietary Chronic Toxicity/Oncogenicity Study With Cga-248757 Technical in Rats: Lab Project Number: F-00068. Unpublished Study Prepared By Ciba-Geigy Corp. 2430 P.
		Mouse-Chronic	Oral	43830015	0.1	37	37	Chang, J.; Morrissey, R. (1995) Cga-248757 Technical: 18-Month Dietary Oncogenicity Study in Mice: Final Report: Lab Project Number: F-00069. Unpublished Study Prepared By Ciba-Geigy Corp. 1530 P.
		Rat-MGR*	Oral	43830016	1.59	388	31.8	Gilles, P.; Hart, S. (1994) A Two-Generation Reproduction Study in Rats With Gca-248757

	Chemical Name	Study Design and species	Administration route	MIRD*	LDT (mg/kg/day)	HDT (mg/kg/day)	LEL (mg/kg/day)	Citation
								Technical: Final Report: Lab Project Number: F-00081. Unpublished Stud Technical: Final Report: Lab Project Number: F-00081. Unpublished Stud Technical: Final Report: Lab Project Number: F-00081. Unpublished Stud
28.	Mesosulfuron-methyl	Mouse-Chronic	Oral	45430403	10.6	1360	1360	Seeberger, A. (2000) Mouse Dietary Oncogenicity (18 months) Study: AE F130060-Substance Technical: Lab Project Number: 2000.0279: 97.0176: C009460. Unpublished study prepared by Aventis Pharma Deutschland GmbH. 1983 p.
29.	Oxadiazon	Rat-Chronic	Oral	149003	0.5	193	50.9	Kudo, S.; Takeuchi, T.; Hayashi, K.; Et Al. (1981) Twenty-Four Month Chronic Toxicity Study Of Oxiadiazon in Rats. Unpublished Translation Of Study Prepared By Nippon Institute For Biological Science And Institute Of Environmental Toxicology. 1082 P.
30.	Pyrasulfotole metabolite (SXX 0665)	Rat-MGR*	Oral	46246333	2.48	51.9	9.48	PMRA; A Two-Generation Dietary Reproduction Study in Rats Using SXX 0665. Bayer Corporation, Agriculture Division, Stilwell, KS. Study number 91-672-KO, December 4, 2001. MRID 46246333. Unpublished
31.	Rimsulfuron	Rat-Chronic	Oral	42047701	1	568	121	Keller, D. (1991) Combined Chronic Toxicity/ Oncogenicity Study With in E9636-22: Two-Year Feeding Study in Rats: Lab Project Number: 8572-001: 559-90. Unpublished Study Prepared By E.I. Du Pont De Nemours And Co. 1802 P.
32.	Sethoxydim	Mouse-Chronic	Oral	100527	4.48	143	41.2	Takaori, H.; Nishibe, T.; Tsubura, Y.; Et Al. (1981) Chronic Feeding Study Combined With Oncogenicity Study Of Np-55 in Mice. Final Rept. (Unpublished Study Received Apr 15, 1982 Under 7969-58, Prepared By Nippon Soda Co., Ltd., Japan, Submitted By Basf AG
33.	Sulfentrazone	Rat Subchronic	Oral	43004601	3.3	535	199	Nye, D. (1993) Ninety-Day Feeding Study in Rats: F6285 Technical: Lab Project Number: A89-2881: 399: 162AF89143. Unpublished study prepared by FMC Corp. Toxicology Lab. 722 p.
34.	Tepraloxydim	Rat-Subchronic	Oral	44467137	22	440	383	Mellert, W.; Deckardt, K.; Gembardt, C. et al. (1996) Report Reg. No. 191819: Subchronic Oral Toxicity Study in Wistar Rats: Administration in the Diet for 3 Months: Lab Project Number: 31S0459/91048: 96/10756: PCP01749. Unpublished study prepared by BAS AG
35.	Thiazopyr	Rat-Subchronic	Oral	42619722	0.07	227	201	Naylor, M.; Ribelin, W. (1992) Additional Information Related to the Previously Submitted Study: 90 Day Study of MON 13200 Administered in Feed to Albino Rats ML-88-246/EHL 88146 (MRID 42275530): Lab Project Number: ML-88-246/EHL-88146: R.D. NO. 1063: R.D

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	Chemical Name	Study Design and species	Administration route	MIRD*	LDT (mg/kg/day)	HDT (mg/kg/day)	LEL (mg/kg/day)	Citation
Insecticides:								
36.	Buprofezin	Rat-Subchronic	Oral	42935201	3.4	362	316	Watanabe, M.; Todhunter, J. (1992) A 90-Day Oral Toxicity Study of Buprofezin in Rats: Lab Project Number: NNI-BUPROF-EUP-13: T-15. Unpublished study prepared by Preclinical Research Labs and Science Regulatory Services International. 164 p.
37.	Chlorpyrifos-methyl	Mouse-Chronic	Oral	44680602	0.0815	44	41.5	Yoshida, A. Et Al. (1988) Chlorpyrifos-Methyl: 18-Month Oral Toxicity Study in Mice: Lab Project Number: Ghf-R-166. Unpublished Study Prepared By The Institute Of Environmental Toxicology. 934 P.
38.	d-cis, trans-Allethrin	Mouse-Chronic	Oral	41099602	14.4	382	350	Mayfield, R.; Gopinathy, C.; Crook, D.; Et Al. (1989) Pynamin Forte: Potential Tumorigenic Effects in Prolonged Dietary Administration in Mice: Project Id Smo 247/881026. Unpublished Study Prepared By Huntingdon Research Centre Ltd. 980 P.
39.	Fipronil	Rat-Subchronic	Oral	42918643	0.07	24	19.9	Holmes, P. (1993) M&B 46030: Toxicity Study By Dietary Administration To Cd Rats For 13 Weeks: Final Report: Lab Project Number: Rha/298/46030: 90/Rha298/0781: 90/0781. Unpublished Study Prepared By Life Sciences Research Limited. 292 P.
40.	Tetramethrin	Rat-Subchronic	Oral	42146403	5.83	214	57.9	Hosokowa, S.; Hiromori, T.; Seki, T.; et al. (1981) Six-month Subchronic Toxicity Study of Neo-Pynamin Forte in Rats: Lab Project Number: IT-00-0139. Unpublished study prepared by Sumitomo Chemical Co., Ltd. 97 p.
41.	Thiacloprid	Mouse-Chronic	Oral	44927710	5.7	873	234	Wirnitzer, U.; Geiss, V. (1998) YRC 2894: Oncogenicity Study in B6C3F1-Mice Administration in the Food Over 2 Years: Lab Project Number: 27247: T9059195: 108358. Unpublished study prepared by Bayer AG. 2028 p.
Miticide:								
42.	Acequinocyl	Mouse-Chronic	Oral	45531911	2.7	86	7	Waterson, L. (1994) AKD-2023 Technical Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Mice: Lab Project Number: AGK 29/961180. Unpublished study prepared by Huntingdon Life Sciences Ltd. 2100 p. {OPPTS 870.4300}

Chemicals are arranged according in alphabetic order in each class and their LELs, study design and species are provided according to the screened ToxRefDB studies.

* MIRD: Master Record Identifier (specific ID to EPA's Office of Pesticide Programs

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** MGR: Multigeneration Reproductive

Table 2

Solvents, plasticizers, monomers, and Chemical Intermediates associated with fatty liver disease in CEBS.

#	Chemical Name	Study Design and species	Adminstration route	Accession number	LDT	HDT	LEL	Citation
					(mg/kg)			
1.	2,2-Bis(Bromomethyl)-1,3 propanediol	Rat-Chronic	Dosed feed	002-01167-0012-0000-0	25,000	200000	25,000	Toxicology and Carcinogenesis Studies of 2,2-Bis(Bromomethyl)-I,3-Propanediol (Fr-1138 ®), (Cas No. 3296-90-0) in F344/N Rats and B6c3f1 Mice (Feed Studies), U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health
2.	4-Vinyl-1-cyclohexene diepoxide	Rat-Chronic	DERMAL	002-01522-0004-0000-6	50	100	50	Toxicology and Carcinogenesis Studies of 4-Vinyl-L-Cyclohexene Diepoxide (Cas No. 106-87-6) in F344/N Rats And B6c3fi Mice (Dermal Studies), U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health
3.	4,4′-Thiobis(6-tert-butyl-m-cresol)	Mouse-Chronic	Dose feed	002-01472-0005-0000-1	1000	250	250	Toxicology and Carcinogenesis Studies of 4,4′-Thiobis6-tert-butyl-m-cresol) (Cas No. 96-69-5) in F344/N Rats and B6c3fl Mice (Feed Studies), U.S. Department of Health and human services, Public Health Service, National Institutes of Health
4.	Alpha-Methylstyrene	Mouse-Chronic	Respiratory exposure whole body	002-03029-0010-0000-7	600	100	300	Toxicology And Carcinogenesis Studies of α-Methylstyrene (Cas No. 98-83-9) in F344/N Rats And B6c3f1 Mice

#	Chemical Name	Study Design and species	Adminstration route	Accession number	LDT	HDT	LEL	Citation
					(mg/kg)			
								(Inhalation Studies), National Toxicology Pro (Inhalation Studies), National Toxicology Pro (Inhalation Studies), National Toxicology Pro (Inhalation Studies), National Toxicology Pro (Inhalation Studies), National Toxicology Pro (Inhalation Studies), National Toxicology Pro (Inhalation Studies), National Toxicology Pro (Inhalation Studies), National Toxicology Pro (Inhalation Studies), National Toxicology Pro (Inhalation Studies), National Toxicology Pro (Inhalation Studies), National Toxicology Pro (Inhalation Studies), National Toxicology Pro
5.	Dibutyl phthalate	Rat-Short term	Dose feed	002-02002-0020-0000-8	40,000	2,500	5,000	Toxicity Studies of Dibutyl Phthalate (CAS No. 84-74-2) Administered in Feed to F344/N Rats and B6C3F Mice[1], Daniel S. Marsman, D.V.M., Ph.D., Study Scientist, National Toxicology Program, Post Office Box 12233, Research Triangle Park, NC 27709, NIH Publication 95-3353, March 1995, United States Department of Health and Human Services, Public Health Service, National Institutes of Health
6.	Divinylbenzene	Mouse-Chronic	Respiratory exposure whole body	002-02098-0014-0000-6	100	10	10	Toxicology and Carcinogenesis Studies of Divinylbenzene-Hp (Cas No. 1321-74-0) in F344/N Rats And B6c3f1 Mice (Inhalation Studies), National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709, November 2006, NTP TR 534, NIH Publication No. 07-4470, National Institutes of Health, Public Health Service, U.S. Department of

#	Chemical Name	Study Design and species	Adminstration route	Accession number	LDT (mg/kg)	HDT (mg/kg)	LEL (mg/kg)	Citation
								Health And Human Services Health And Human Services
7.	Glycidol	Mouse-Short term	Gavage	002-02212-0017-0000-7	200	25	100	Toxicology and Carcinogenesis Study of Glycidol (Cas No. 556-52-5) in Genetically Modified Haploinsufficient P16ink4a/P19arf Mice (Gavage Study), National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709, November 2007, NTP GMM 13, NIH Publication No. 08-5962, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services
8.	Isoprene	Rat-Chronic	Respiratory exposure whole body	002-02324-0012-0000-6	7000	70	220	Isoprene (CAS No. 78-79-5) Administered by Inhalation to F344/N Rats And B6C3F Mice 1, Ronald L. Melnick, Ph.D., Study Scientist, National Toxicology Program, Post Office Box 12233, Research Triangle Park, NC 27709, NIH Publication 94-3354, July 1994, United States Department of Health and Human Services, Public Health Service, National Institutes of Health
9.	Resorcinol	Rat-Chronic	Gavage	002-02771-0007-0000-6	150	50	50	Toxicology and Carcinogenesis Studies of Resorcinol (Cas No. 108-46-3) in F344/N Rats And B6c3f1 Mice (Gavage Studies), U.S. Department Of Health And Human Services, Public Health Service,

#	Chemical Name	Study Design and species	Adminstration route	Accession number	LDT	HDT	LEL	Citation
					(mg/kg)			
								National Institutes of Health National Institutes of Health
10.	Sodium selenite	Rat-Short Term	Dosed water	002-02833-0003-0000-1	32	2	4	Toxicity Studies of Sodium Selenate and Sodium Selenite (Cas Nos. 13410-01-0 And 10102-18-8) Administered in Drinking Water to F344/N Rats And B6c3f1 Mice, Kamal M. Abdo, Ph.D., Study Scientist, National Toxicology Program, Post Office Box 12233, Research Triangle Park, NC 27709, NIH Publication 94-3387, July 1994, United States Department of Health and Human Services, Public Health Service, National Institutes of Health
11.	Tetrabromobisphenol A	Mouse-Short Term	Gavage	002-02872-0004-0000-5	1000	10	100	_____
12.	Tetrafluoroethylene	Rat-Chronic	INHALATION	002-02886-0006-0000-2	1250	156	156	Toxicology and Carcinogenesis Studies of Tetrafluoroethylene (Cas No. 116-14-3) in F344/N Rats And B6c3f Mice1 (Inhalation Studies), National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709, April 1997, NTP TR 450, NIH Publication No. 97-3366, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health
13.	Tricresyl phosphate	Rat-Chronic	Dosed feed	002-02950-0007-0000-5	600	75	75	Toxicology and Carcinogenesis, Studies of Tricresyl Phosphate, (Cas No. 1330-78-5), in F344/N Rats And

#	Chemical Name	Study Design and species	Adminstration route	Accession number	LDT	HDT	LEL	Citation
					(mg/kg)			
								B6c3f, Mice, (Gavage And Feed Studies), Nat B6c3f, Mice, (Gavage And Feed Studies), Nat B6c3f, Mice, (Gavage And Feed Studies), Nat B6c3f, Mice, (Gavage And Feed Studies), Nat B6c3f, Mice, (Gavage And Feed Studies), Nat
14.	Trimethylolpropane triacrylate	Rat-Chronic	Skin application	002-02968-0017-0000-5	0.3	1	0.3	Toxicology and Carcinogenesis Studies of Trimethylolpropane Triacrylate, (Technical Grade), (Cas No. 15625-89-5) in F344/N Rats And B6c3f1/N Mice, Dermal Studie, National Toxicology Program, Research Triangle Park, NC 27709, December 2012
15.	Vinyl toluene	Rat-Chronic	Respiratory exposure whole body	002-03003-0004-0000-2	300	100	100	Toxicology and Carcinogenesis Studies of Vinyl Toluene (Mixed Isomers) (65%–71% Meta-Isomer And 32%–35% Para-Isomer) (Cas No. 25013-15-4) in F344/N Rats And B6c3f1 Mice (Inhalation Studies), U.S. Department of Health And Human Services, Public Health Service, National Institutes of Health
		Mouse-Chronic	Respiratory exposure whole body	002-03003-0005-0000-3	25	10	25	
16.	1-Amino-2,4-dibromoanthraquinone	Rat-Chronic	Dosed feed	002-01108-0006-0000-8	20,000	2,000	20,000	Toxicology and Carcinogenesis Studies of 1-Amino-2,4-Dibromoanthraquinone (Cas No. 81-49-2) in F344/N Rats And B6c3f1 Mice (Feed Studies), U.S. Department Of Health And Human Services, Public Health Service, National Institutes of Health
17.	4,4′-Diamino-2,2′-stilbenedisulfonic acid, disodium salt	Mouse-Chronic	Dosed feed	002-01460-0001-0000-4	12500	6250	6250	Toxicology and Carcinogenesis Studies of 4,4′-Diamino-2,2′-Stilbenedisulfonic Acid, Disodium Salt

#	Chemical Name	Study Design and species	Adminstration route	Accession number	LDT (mg/kg)	HDT (mg/kg)	LEL (mg/kg)	Citation
								(Cas No. 7336-20-1) in F344/N Rats and B6c3 (Cas No. 7336-20-1) in F344/N Rats and B6c3 (Cas No. 7336-20-1) in F344/N Rats and B6c3 U.S. Department of Health And Human Services, Public Health Service, National Institutes of Health
18.	p-Nitrobenzoic acid	Mouse-Chronic	Dosed feed	002-03178-0010-0000-2	5000	1250	1250	Toxicology and Carcinogenesis Studies of P-Nitrobenzoic Acid (Cas No. 62-23-7) in F344/N Rats And B6c3fl Mice (Feed Studies), U.S. Department of Health And Human Services, Public Health Service, National Institutes of Health
19.	p-Nitrotoluene	Mouse	Dosed feed	002-02576-0015-0000-8	5000	1250	1250	Toxicology and Carcinogenesis Studies of P-Nitrotoluene (Cas No. 99-99-0) in F344/N Rats And B6c3f1 Mice (Feed Studies) National Toxicology Program, P.O. Box 12233, Research Triangle Park, Nc 27709, May 2002, NTP TR 498, NIH Publication No. 02-4432, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health
20.	2-Methylimidazole	Rat-Chronic	Dosed feed	002-01360-0011-0000-4	5000	300	1000	Toxicology and Carcinogenesis Studies of 2-Methylimidazole (Cas No. 693-98-1) in F344/N Rats And B6c3f1 Mice (Feed Studies), National Toxicology Program, P.O. Box 12233, Research Triangle Park, Nc 27709, December 2004, NTP TR 516, NIH

#	Chemical Name	Study Design and species	Adminstration route	Accession number	LDT (mg/kg)	HDT (mg/kg)	LEL (mg/kg)	Citation
								Publication No. 05-4456, U.S. Department of
								Publication No. 05-4456, U.S. Department of
								Publication No. 05-4456, U.S. Department of
								Publication No. 05-4456, U.S. Department of
								Publication No. 05-4456, U.S. Department of
								Publication No. 05-4456, U.S. Department of
								Publication No. 05-4456, U.S. Department of
21.	Methyl isobutyl ketone	Mouse-Chronic	Respiratory exposure whole body	002-02438-0003-0000-2	1800	450	900	Toxicology and Carcinogenesis Studies of Methyl Isobutyl Ketone (Cas No. 108-10-1) in F344/N Rats And B6c3f1 Mice (Inhalation Studies), National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709, February 200, NTP TR 538, NIH Publication No 07-4476, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services
22.	Toluene	Rat-Chronic	Respiratory exposure whole body	002-02916-0005-0000-5	1200	600	600	Toxicology and Carcinogenesis Studies of Toluene (Cas No. 108-88-3) in F344/N Rats And B6c3fi Mice (Inhalation Studies), U.S. Department of Health And Human Services, Public Health Service National Institutes of Health
		Mouse-Chronic	Respiratory exposure whole body	002-02916-0006-0000-6	1200	120	600	
23.	Barium chloride dehydrate	Rat-Chronic	Dosed water	002-01684-0004-0000-5	2500	500	500	Toxicology and Carcinogenesis Studies of Barium chloride dihydrate (Cas No. 10326-27-9) In F344/N Rats And B6c3fl Mice (Drinking Water Studies), U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National

#	Chemical Name	Study Design and species	Adminstration route	Accession number	LDT (mg/kg)	HDT (mg/kg)	LEL (mg/kg)	Citation
								Toxicology Program, Technical Report Series Toxicology Program, Technical Report Series Toxicology Program, Technical Report Series
24.	Styrene-acrylonitrile trimer	Rat-Short term	Dosed feed	002-02846-0004-0000-6	4000	250	250	Toxicology and Carcinogenesis Study of Styrene-acrylonitrile trimer in F344/N Rats (Perinatal And Postnatal Feed Studies), National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709, July 2012, NTP TR 573, NIH Publication No. 12-5915, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services
25.	Decalin	Mouse-Chronic	Respiratory exposure whole body	002-01965-0013-0000-7	400	25	100	Toxicology and Carcinogenesis Studies of Decalin (Cas No. 91-17-8) in F344/N Rats and B6c3f1 Mice and a Toxicology Study of Decalin In Male NBR Rats (Inhalation Studies), National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709, January 2005, NTP TR 513, NIH Publication No. 05-4447, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health
26.	3,3′-Dimethoxybenzidine dihydrochloride	Rat-Chronic	Dosed water	002-01389-0009-0000-2	330	80	80	Toxicology and Carcinogenesis Studies of 3,3′-Dimethoxybenzidine dihydrochloride (Cas No. 20325-40-0) in F344/N Rats (Drinking Water Studies), U.S.

#	Chemical Name	Study Design and species	Adminstration route	Accession number	LDT (mg/kg)	HDT (mg/kg)	LEL (mg/kg)	Citation
								Department of Health And Human Services, P Department of Health And Human Services, P Department of Health And Human Services, P Department of Health And Human Services, P Department of Health And Human Services, P
27.	Bis(2-Chloroethoxy)methane	Rat-Chronic	Skin application	002-03051-0014-0000-6	300	75	75	Toxicology and Carcinogenesis Studies of Bis(2-chloroethoxy)methane (Cas No. 111-91-1) in F344/N Rats and B6c3f1 Mice (Dermal Studies), National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709, August 2011, NTP TR 536, NIH Publication No. 11-5904, National Institutes of Health Public Health Service, U.S. Department of Health And Human Services
28.	1-Bromopropane	Mouse-Chronic	Respiratory exposure whole body	002-01113-0014-0000-3	250	62.5	62.5	Toxicology and Carcinogenesis Studies of 1-Bromopropane (Cas No. 106-94-5) in F344/N Rats And B6c3f1 Mice (Inhalation Studies), National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709, August 2011, NTP TR 564, NIH Publication No. 11-5906, National Institutes of Health Public Health Service, U.S. Department Of Health And Human Services
29.	Tribromomethane	Mouse-Chronic	Gavage	002-02934-0011-0000-2	200	50	50	Toxicology And Carcinogenesis Studies of Tribromomethane (Bromoform) (Cas No. 75-25-2) in F344/N Rats And B6c3fi Mice

#	Chemical Name	Study Design and species	Adminstration route	Accession number	LDT	HDT	LEL	Citation
					(mg/kg)			
								(Gavage Studies), U.S. Department of Health (Gavage Studies), U.S. Department of Health (Gavage Studies), U.S. Department of Health (Gavage Studies), U.S. Department of Health (Gavage Studies), U.S. Department of Health (Gavage Studies), U.S. Department of Health
30.	Sodium dichromate dihydrate (VI)	Rat-Chronic	Dosed water	002-02819-0022-0000-6	516 mg/L	14.3 mg/L	14.3 mg/L	The Toxicity Studies of Sodium dichromate dehydrate (Cas No. 7789-12-0) Administered in Drinking Water to Male and Female F344/N Rats And B6c3f1 Mice and Male BALB/C And Am3-C57bl/6 Mice, January 2007, National Institutes of Health, Public Health Service, U.S. Department of Health And Human Services
31.	1,2-Dihydro-2,2,4-trimethylquinoline (monomer)	Mouse-Long term	Dermal	002-01051-0016-0000-6	10	3.6	3.6	_____

Chemicals are arranged in alphabetic order and their LELs, study design and species are provided according to the screened CEBS studies.

Table 3

Miscellaneous chemicals associated with fatty liver disease in CEBS.

#	Chemical Name	Study Design and species	LEL
1.	Polysorbate 80	Rat-Chronic	25,000 mg/kg
2.	T-Butylhydroquinone	Mouse-Chronic	1,250 mg/kg
3.	Benzophenone	Rat-Chronic	312 mg/kg
4.	Cumene hydroperoxide	Rat-Short term	100 mg/kg
5.	Isobutyl nitrite	Mouse-Chronic Rat-Chronic	37.5 mg/kg
6.	N,N-Dimethyl-p-toluidine	Rat-Chronic	6 mg/kg
7.	Sodium azide	Rat-Chronic	5 mg/kg
8.	Tetranitromethane	Rat-Chronic	2 mg/kg
9.	Vanadium oxide	Mouse-Chronic	1 mg/M3
10.	Nickel (II) oxide	Rat-Chronic	0.63 mg/m3
11.	Nickel sulfate hexahydrate	Rat-Chronic	0.25 mg/m3
12.	Indium phosphide	Rat-Chronic	0.03 mg/m3
13.	Gallium arsenide	Rat-Chronic	0.01 mg/M3
14.	3,3′-Dimethylbenzidine dihydrochloride	Rat-Chronic	0.003**

Chemicals are arranged in alphabetic order and their LELs, study design and species are provided according to the screened CEBS studies.

** Units were not provided in the CEBS search.

Table 4

Pesticides associated with fatty liver disease in CEBS.

#	Chemical Name	Study Design and species	LEL (mg/kg)
1.	1,2-Dibromo-2,4-dicyanobutane	Rat-Chronic	2
2.	1,2,3-Trichloropropane	Mouse-Chronic	6
3.	1,2,3-Trichloropropane	Rat-Chronic	3
4.	3,3′,4,4′-Tetrachloroazobenzene	Rat-Chronic	10
5.	Beta-Picoline	Rat-Chronic	312.5 mg/L
6.	Formamide	Rat-Chronic	20
7.	Fumonisin B1	Mouse-Chronic	80
8.	Hexachloroethane	Rat-Chronic	10
9.	Monochloroacetic acid	Rat-Chronic	10
10.	Naphthalene	Rat-Chronic	10
11.	p,p′-Dichlorodiphenyl sulfone	Mouse-Chronic	30
12.	Triethanolamine	Mouse-Chronic	630

Pesticides are arranged in alphabetic order and their LELs, study design and species are provided according to the screened CEBS studies.

Table 5

Fragrances, cosmetics and essential oils associated with fatty liver disease in CEBS.

#	Chemical Name	Study Design and species	LEL (mg/kg)
1.	3,4-Dihydrocoumarin	Mouse-Chronic	200
2.	Beta-Myrcene	Mouse-Chronic	250
3.	Dipropylene glycol	Rat-Chronic	25,000
4.	Estragole	Mouse-Short term	37.5
5.	Hydroquinone	Rat-Chronic	25
6.	Isoeugenol	Rat-Chronic Mouse-Chronic	75
7.	Methyl trans-styryl ketone	Mouse-Chronic	10
8.	Methyleugenol	Rat-Short term	150
9.	Tris(2-Chloroethyl) phosphate	Rat-Chronic	44

Chemicals are arranged in alphabetic order and their LELs, study design and species are provided according to the screened CEBS studies.

Table 6

Paints, polishes, dyes and food additives associated with fatty liver disease in CEBS.

#	Chemical Name	Study Design and species	LEL (mg/kg)
1.	2-Butoxyethanol	Rat-Chronic	31.2
2.	2,4-Diaminophenol dihydrochloride	Mouse-Chronic	0.038
3.	Benzyl acetate	Rat-Chronic	3,000
4.	C.I. Acid red 114	Rat-Chronic	0.007
5.	C.I. Direct blue 15	Rat-Chronic	0.125**
6.	C.I. Direct blue 218	Rat-Chronic Mouse-Chronic	1,000
7.	HC yellow 4	Rat-Chronic	25,000
8.	Malachite green	Rat-Chronic	600
9.	Pyrogallol	Rat-Chronic	5

Chemicals are arranged in alphabetic order and their LELs, study design and species are provided according to the screened CEBS studies.

** Units were not provided in the CEBS search.

Table 7

PCBs and dioxin-like compounds associated with fatty liver disease in CEBS.

#	Chemical Name	Study Design and species	LEL (mg/kg)
1.	2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	Rat-Chronic	0.01
2.	Dioxin mixture	Rat-Chronic	10
3.	PCB 118	Rat-Chronic	0.1
4.	PCB 126	Rat-Chronic	0.00001
5.	PCB 153	Rat-Chronic	0.01
6.	Pentachlorodibenzofuran (PECDF)	Rat-Chronic	0.000006

Chemicals are arranged in alphabetic order and their LELs, study design and species are provided according to the screened CEBS studies.