Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guideline: Occupational liver diseases☆

European Association for the Study of the Liver*

Summary

A variety of chemicals have been linked to occupational liver diseases, including several solvents and mixtures thereof, pesticides, and metals. Workplace exposures have been associated with virtually the entire spectrum of acute and chronic liver diseases. However, their prevalence is inadequately quantified and their epidemiology limited. Occupational liver diseases may result from high accidental or from prolonged lower level exposures. Whereas the former is uncommon and easily recognised, the latter are relatively more frequent but often overlooked because they may display normal values of conventional markers, have an insidious onset and be asymptomatic or be obfuscated and confounded by concurrent conditions. In addition, specific tests of toxicity are not available, histopathology may not be revealing and the assessment of internal dose of chemicals is usually not decisive. Given these circumstances, the diagnosis of these liver disorders is challenging, one of exclusion and often requires an interdisciplinary approach. These recommendations offer a classification of the type of liver injuries associated with occupational exposures – based in part on the criteria for drug-induced liver injury – a grading of their severity, and the diagnostic and preventive criteria for chemically induced occupational liver disease.

Introduction

Occupational exposures can induce liver injury in a similar way to prescription drugs, herbal and dietary supplements, and workplace exposure has been implicated in the full spectrum of liver disease. However, the awareness of hepatologists for this specific aetiology of liver injury is limited and the incidence and prevalence of occupational liver diseases (OLDs) remains unknown. Acute liver injury is likely to decrease, at least in high income countries, given the improvement in health and safety in workplaces achieved over the recent years. Unpredictable routes of exposure such as breakdown, cleaning and maintenance of machinery, and accidental leakage still occur though and new causes of OLD will potentially come to light, such as liver silicosis, particulate matter air pollution and increasing use of nanomaterials.[1–3] Moreover, the diagnosis of OLD remains challenging in clinical practice due to the lack of pathognomonic signs and sensitive biomarkers of liver injury. Whilst acknowledging that viral infections in hospital workers are recognised as OLDs, herein, attention will only be paid to chemically induced liver injuries.

These recommendations are intended to provide standardisation of nomenclature, definitions and classification of the type of liver injuries, based in part on the criteria for drug-induced liver injury (DILI), which attempt to grade their severity.[4,5] The main focus will be to increase awareness of OLDs within the medical community and to improve recognition and management of affected patients in a consistent manner.

Due to the absence of data on observational studies and meta-analyses or systematic reviews, the evidence and recommendations in these guidelines have been graded according to the Oxford Centre for Evidence-based Medicine, which assesses evidence according to diagnostic, prevalence, aetiological, prognostic or preventive categories,[6] and – even when the evidence is inconclusive – can still generate grades of recommendation. This follows the recent recommendations for European Association for the Study of the Liver (EASL) Clinical Practice Guidelines (CPGs).[7]

This CPG has been developed along a 2-year mandate by a panel of experts chosen by the EASL Governing Board who had 3 face to face meetings. This included experts in hepatology, toxicology, pharmacology, pathology, occupational medicine and epidemiology. Conflicts of interest were declared as requested, and consensus was reached by discussion, whenever required. The recommendations were peer-reviewed by external expert reviewers and approved by the EASL Governing Board. The CPG was developed using data collected from PubMed and Cochrane database searches up to December 2018. The searches were conducted using the terms "liver diseases, occupational", "hepatotoxicity", "drug-induced liver injury", and "chemicals", "toxicants", "vinyl chloride", "TASH", "NAFLD". Papers were searched for additional references. No other restrictions were applied. This CPG is based, as far as possible, on evidence from existing publications and, when unavailable, the authors provided personal experiences and opinions and reached a unanimous expert consensus.

Epidemiology

Despite the well-documented presence of multiple potentially hepatotoxic chemicals at a variety of workplaces (*e.g.*, agricultural, hospitals, dry cleaning shops, chemical factories covering polymer synthesis, resins, leather and printing) the prevalence of OLD is unknown. We will address the role of occupational risk factors as they contribute to non-malignant and malignant liver

Received 12 August 2019; accepted 12 August 2019

☆ **Clinical Practice Guideline Panel:** Chair: Massimo Colombo; Panel members: Carlo La Vecchia, Marcello Lotti, M. Isabel Lucena, Christophe Stove, Valérie Paradis; EASL Governing Board representative: Philip Newsome.

* Corresponding author. Address: European Association for the Study of the Liver (EASL), The EASL Building – Home of Hepatology, 7 rue Daubin, CH 1203 Geneva, Switzerland. Tel.: +41 (0) 22 807 03 60; fax: +41 (0) 22 328 07 24.

Please cite this article in press as: European Association for the Study of the Liver. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.08.008

Box 1. Summary of epidemiological studies on occupational liver disease.

a. Non-malignant liver diseases

Data are insufficient to provide recommendations, due to difficulties in adjusting for covariates and confounding factors.

b. Liver neoplasms

i. Vinyl chloride monomer and angiosarcoma of the liver and hepatocellular carcinoma

Following the control of occupational exposure to VCM in the mid-1970s, few additional cases of VCM-related angiosarcoma of the liver are anticipated in the future. By inference, this applies to other liver cancers, too.

Surveillance with ultrasounds for development of emergent liver neoplasms should be discussed for workers exposed to high levels of VCM in the past, *i.e.* until the mid-1970s, as defined by their job title (reactor cleaners).

ii. Controversial associations with liver cancers

The available evidence does not support recommendations for screening for liver cancers in trichloroethylene and other chlorinated solvent-exposed workers, workers exposed to polychlorinated biphenyl and workers exposed to pesticides.

conditions. A summary of the main conclusions and recommendations is shown in Box 1.

Non-malignant liver diseases

In a population survey of over 13,700 workers from Taiwan, higher prevalence rates of self-reported unspecified "liver disease" were observed among blue-collar or unskilled workers, although notably they also reported more frequent tobacco and alcohol use,[8] raising uncertainty about causation. Substantially higher mortality rates from non-neoplastic diseases of the liver were also reported in low versus high social class occupations in a Korean cohort of workers enrolled in the national employment insurance program between 1995 and 2000.[9] Similarly, using 1979–1981 data, the California Occupational Mortality Study (COMS) reported a high mortality from cirrhosis among selected low social class occupations, including bartenders, loggers, laborers, roofers, construction workers, farm workers, ironworkers and painters for men, and waitresses, telephone operators, cosmetologists, dress makers, hospital orderlies, textile workers and laborers for women. Conversely, a low mortality from cirrhosis was observed among high social class occupations.[10] An elevated mortality from cirrhosis was observed among publicans and bar staff of both sexes, and male seafarers, caterers, cooks and kitchen porters in an analysis of national English and Welsh death data.[11] Overall, these findings point to unfavourable lifestyle factors linked to lower social class, in particular alcohol abuse and tobacco smoking, which may coexist with exposure to other occupational toxins.

However, one of the challenges can be the presence of confounding factors. As an example, an excess risk of cirrhosis following high cumulative exposure to vinyl chloride monomer (VCM) in the workplace was suggested by a re-analysis of European workers, albeit in the absence of a linear trend in risk or of an excess mortality from cirrhosis.[12] However, incorrect associations can often be made when conclusions are drawn from single studies. A systematic review and meta-analysis including data from the aforementioned European multicentre study,[12] along with a large multicentre collaborative re-analysis from North America[13] and 5 smaller independent cohort studies, of over 40,000 VCM-exposed workers with 203 deaths from cirrhosis,[14] did not find any increased mortality from cirrhosis in VCM-exposed workers overall. The pooled relative risk (RR) was 0.73 (95% CI 0.61–0.83), with no evidence of heterogeneity or publication bias. Thus, the available epidemiological data do not support a relationship between occupational exposure to VCM and cirrhosis,[15] which is in agreement with experimental studies of VCM-exposed rodents and pathology reports of VCM-exposed workers and patients with VCM-related liver angiosarcoma. These studies did not observe evidence of cirrhosis, only periportal fibrosis.[16–19]

In another example, despite prior experimental data associating shift work with non-alcoholic fatty liver disease (NAFLD),[20,21] a cross-sectional study based on multiple cycles of the National Health and Nutrition Examination Survey (NHANES) cohort found no evidence of an association when comparing 1,019 shift-workers with 8,159 other adults (odds ratio 1.11, 95% CI 0.87–1.43.)[22] Circadian disruption (jet lag) has been related to hepatocellular carcinoma (HCC) in rodents, possibly through induction of NAFLD.[21] Data on shift work and liver neoplasms in humans, however, are inconclusive.

Data are insufficient to provide recommendations due to difficulties in adjusting for covariates and confounding factors.

Liver malignancies

Vinyl chloride monomer and angiosarcoma of the liver and hepatocellular carcinoma

Since the first 3 reported cases of liver angiosarcoma amongst VCM reactor cleaners in a US facility,[23] subsequent evidence has confirmed the causative link between high occupational exposure to VCM (among autoclave workers) and angiosarcoma of the liver.[12,13] In the most recent update, a collaborative re-analysis of nearly 10,000 US workers exposed to VCM reported 63 deaths from angiosarcoma of the liver, occurring after an average of 40 years of follow-up.[13] With reference to HCC, the International Agency for Research on Cancer (IARC) concluded in 1987 that VCM exposure causes HCC,[24,25] in part based on data from 2 large collaborative re-analyses of VCM-exposed European[12] and US workers.[13] A meta-analysis of data from these 2 large cohorts estimated a summary RR of 1.35 for liver cancers other than angiosarcomas, which was of borderline significance (95% CI 1.04–1.77). This estimate was based on 60 deaths mainly from HCC but also from liver cancer of unspecified or undefined histology, and hence possibly angiosarcomas.[26,27] It is therefore unclear if the excess risk was real or due to misclassification of HCC.[12,15] In any case, in 2012, the IARC confirmed its earlier conclusion on VCM exposure as a causal factor for HCC.[24,25] In 2017, a US collaborative re-analysis provided results updated up to 2013 and, based on 32 deaths from the disease, found that the increased risk of HCC was restricted to workers with very high estimated cumulative

Please cite this article in press as: European Association for the Study of the Liver. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.08.008

exposures, *i.e.* over 1,000 ppm-years – approximately 25 times a working lifetime (40 years) at the exposure limit of 1.0 ppm.[13] More recently, an ecologic investigation from Texas found a positive association between the incidence of HCC and VCM concentrations in air[28] – in this case the exposure was environmental though and not occupational. In conclusion, whilst high VCM exposure has a clear causative association with angiosarcoma of the liver, its link with HCC is not as well-established.[15] Following the control of occupational exposure to VCM in the mid-1970 s, few additional cases of VCM-related angiosarcoma of the liver are anticipated in the future. By inference, this applies to other liver cancers too.

Recommendation

- Surveillance with ultrasound for development of emergent liver neoplasms should be discussed for workers exposed to high levels of VCM in the past, *i.e.* until the mid-1970s, as defined by their job title (reactor cleaners). **Grade D**
  Evidence: Extrapolation from level 2 studies (historic cohort studies)

Controversial associations with liver cancers

Trichloroethylene. Trichloroethylene (TCE), which has been widely used for decades to degrease metal parts and for dry cleaning,[29] when given at very high doses to certain strains of rats and mice can induce a variety of cancers, including liver/kidney tumours, and lymphomas.[30] The evidence from epidemiologic studies is less clear. A meta-analysis combining results from 9 cohort studies (generally based on fewer than 10 events) found a modest association for overall TCE exposure and cancer of the liver or gallbladder/biliary tract (pooled RR 1.29, 95% CI 1.07–1.56). However, there was no consistent dose-risk relationship as the estimate for the highest TCE exposure category (RR 1.28, 95% CI, 0.93–1.77) was similar to that of the overall analysis.[31] The pooled RR from the 3 studies providing information on liver cancer alone fell short of finding an association (pooled RR 1.25, 95% CI 0.99–1.57).[32] A nested case-control study from the Nordic record-linkage study did not find an increased liver cancer risk among dry cleaners when TCE was the dominant solvent,[33] in agreement with a US cohort of over 5,000 dry cleaning workers.[34]

Tetrachloroethylene (or perchloroethylene). A record-linkage study from 4 Nordic countries based on census occupation information (*i.e.* the Nordic Country Occupational Cancer, NOCCA, study) suggested an association between occupational exposure to TCE or perchloroethylene (also named tetrachloroethylene), a chlorinated solvent mainly used in dry cleaning, and HCC.[35]

A systematic review by the U.S. Environmental Protection Agency that included 18 studies which used different exposure-assessment approaches (*e.g.* individual exposure assigned using a job-exposure matrix; individuals employed only in facilities using tetrachloroethylene as the primary solvent exposure; occupational title as dry cleaner, launderer or presser as a surrogate of tetrachloroethylene exposure), did not find a consistent association, even among studies with a large number of observed events/exposed cases or a strong exposure-assessment approach.[36]

Polychlorinated biphenyl exposure. A meta-analysis of occupational exposure to polychlorinated biphenyls (PCBs) found no significant association with liver cancer (pooled standardized mortality ratio [SMR] = 1.26, 95% CI 0.65–2.20), although this was based on only 12 events from 4 investigations.[37] An excess mortality from liver, gallbladder and biliary tract cancers was detected in a cohort of US PCB-exposed workers, based on 5 deaths among men and 9 among women,[38] but this was only significant in women. Similarly, no increase in mortality from liver cancer was reported in an updated analysis of 2 Italian occupational cohorts.[39] A combined analysis of the 3 largest US capacitor manufacturing cohorts, including overall 24,865 workers exposed to PCBs from 1938 to 1977 at plants in Indiana,[40] Massachusetts, and New York,[41] with 63 deaths from liver, biliary tract and gallbladder cancer also found no excess liver cancer mortality overall (SMR 0.98, 95% CI 0.76–1.26), irrespective of longer (≥90 days of employment) or higher cumulative PCB exposure (≥600,000 unit-days).[42] Thus, epidemiologic evidence does not support an association between occupational exposure to PCBs and liver cancer risk. Yet, PCBs are currently classified as Group 1 "Carcinogenic to humans" by IARC,[43] largely based on evidence of melanoma risk in humans.

Pesticides. In the Agricultural Health Study cohort[44] there was an excess HCC risk in metolachlor (a widely used herbicide) users, but there were only 23 exposed cases, and the RR for the highest intensity-weighted lifetime days exposure category was significant only when non-exposed applicators were used for comparison (RR = 3.18, 95% CI 1.10–9.22). Other herbicides and pesticides were occasionally associated with slight changes in liver function and enzymes,[45,46] and also to HCC risk, but the evidence was inconsistent.[47] In a systematic review from 2015, including 15 studies on pesticide exposure and liver cancer (mainly HCC), most studies, particularly those relying on self-reported exposure and occupation, job-exposure matrices, and rural residence, found no association.[48] In addition, a Canadian cohort of over 2 million agricultural workers found, if anything, a reduced liver cancer occurrence.[49] However, biomarker-based studies conducted on Chinese populations suggested that certain organochlorine serum levels, mainly of dichlorodiphenyl trichloroethane (DDT), may be associated with an increased liver cancer risk.[50–52]

Various jobs. In a cohort of over 8 million Koreans followed for an average of 11 years, higher mortality rates from liver and intrahepatic bile duct cancers were observed in both male and female of lower social class groups.[9] Similarly, male cooks and kitchen porters, caterers, publicans and bar staff, and seafarers had a higher mortality from liver cancer in an analysis of national mortality data from England and Wales, which has been attributed to higher levels of alcohol consumption in those occupations compared to the general population.[11] A record-linkage study of 15 million adults from 5 Nordic countries identified 17,730 HCC cases in men and 10,973 in women in the 1960–90 censuses that were followed-up until 2005.[53] Of note, the highest standardised incidence ratios (SIR) in men were

Please cite this article in press as: European Association for the Study of the Liver. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.08.008

observed among waiters (4.22, 95% CI 3.47–5.13), cooks and stewards (SIR = 2.6, 95% CI 1.9–3.3) and beverage workers (SIR = 2.5, 95% CI 1.85–3.31).[53] Other significant high-risk job categories included journalists, seamen, administrators, sale/shop workers, plumbers and economically inactive subsets. In women, excess risks were seen amongst smelting workers (SIR = 2.11, 95% CI 1.09–3.68), tobacco workers (SIR = 2.04, 95% CI 1.08–3.48), waitresses (SIR = 1.36), launderers and dry cleaners (SIR 1.27) and building caretakers (SIR 1.21). Whilst the pattern of high-risk occupations in men largely reflects the high frequency of alcohol consumption and other known lifestyle risk factors for HCC (*e.g.* tobacco and hepatitis), chemical factors may at least in part contribute to the highest SIR observed in women.[53] Based on Finnish data, Lindbohm *et al.* reported excess risks of liver cancer among workers highly exposed to chlorinated hydrocarbons and other solvents, though based on a limited number of exposed individuals.[54] Similarly, an excess of liver cancer was observed in a Danish cohort of 15,534 men and 3,593 women working in the printing industry in 1970.[55] A US case-control study conducted in 1975–1980 and including 265 HCC cases, found an excess liver cancer risk for male farm labourers and males employed in winemaking, gasoline service stations, laundering, bartenders and other eating and drinking places.[56] Another US retrospective study with over 1,700 deaths from liver cancer found an increased risk for oil refinery workers, plumbers and pipe fitters, textile workers, butchers and meat cutters and cooks.[57] Similarly a Danish nested case-control study with almost 1,000 liver cancer cases found an excess risk in a large number of industries, including the printing industries and among employees with easy access to alcoholic drinks.[58] A follow-up study based on the Swedish Family-Cancer Database found increased liver cancer risks for male sales agents, journalists, seamen, waiters, cooks and female beverage manufacture workers.[59] Two case-control studies, 1 in Italy and 1 in France, also found associations between HCC and employment in repair of motor vehicles.[60] and metal machining jobs.[61] A Japanese study on 51 offset colour proof-printing workers exposed to 1,2-dichloropropane and/or dichloromethane reported 11 cases of cholangiocarcinoma. Despite this cluster, no further reports are available on 1,2-dichloropropane and/or dichloromethane.[62]

A narrative review reported associations between polycyclic aromatic hydrocarbons and liver cancer, besides solvents and asbestos, with however inconsistent findings across original reports, and unsatisfactory mechanistic justification for asbestos. There were also scattered reports of an association between heavy metals and NAFLD.[63]

We should call for raised attention on unexpected clusters of OLD and new work-related health risks in general, as the only way to establish epidemiological links is to have such reports made publicly available.

The available evidence does not support recommendations for screening for liver cancers in trichloroethylene and other chlorinated solvent-exposed workers, workers exposed to polychlorinated biphenyl and workers exposed to pesticides.

The occupational setting

A wide variety of chemicals, encountered at the workplace, have been linked to liver injury. Table 1 provides a list of compounds, with the associated liver pathologies, which are further elaborated on in Section 6. Table 2 links these compounds to (typical) usages, which may be further linked to professions in which these compounds are (or can be) encountered. The latter is particularly relevant to allow a suspicion to be raised between workplace-related exposure to a liver toxicant (even when

Table 1. Pathological patterns and morphological features of liver disease associated with workplace-related toxicants.

Pathological patterns	Morphological features	Toxicants
Acute damage		
Hepatocellular	Hepatocellular necrosis ± lobular inflammation	CCl_4, chloroform, toluene, TNT, PCBs, chloronaphthalene, DMF, hydrazine, 2-nitropropane, phosphorus, DMA, halothane, TCE, tetrachloroethane, 1,4-dichlorobenzene
	Microvesicular steatosis	DMF
Cholestatic/mixed	Cholestasis, cholangitis Combined features	Methylenedianiline Nitrobenzene, paraquat, methylenedianiline
TAFLD	Steatosis (macro/microvesicular) Steato-hepatitis (steatosis + lobular inflammation + hepatocellular ballooning)	Chloroalkenes (PCE, TCE), VCM, chloroform, CCl_4, volatile organic compounds (benzene, toluene, styrene, xylene), dioxins, chlordecone, DMF, hydrazine, arsenic, mercury, POPs, pesticides, and some nitro-organic compounds
Vascular	Sinusoidal obstruction syndrome Peliosis	VCM, dioxin, pyrrolizidine alkaloids, arsenic, copper sulfate VCM
Chronic damage		
Fibrosis	Periportal fibrosis Extensive fibrosis/cirrhosis	VCM, PCBs, chloronaphthalene, Tetrachloroethane VCM
Vascular	Porto-sinusoidal vascular disease (previously hepatoportal sclerosis)	VCM, sprays containing copper sulfate and lime
Tumors		
Epithelial		
Hepatocellular carcinoma		Arsenic, dimethylnitrosamine
Cholangiocarcinoma		1,2-Dichloropropane, dichloromethane
Vascular		
Angiosarcoma		VCM, Arsenic
Epithelioid hemangioendothelioma		VCM

DMF, dimethylformamide; PCBs, polychlorinated biphenyls; POPs, persistent organic pollutants; TCE, trichloroethylene; VCM, vinyl chloride monomer.

Please cite this article in press as: European Association for the Study of the Liver. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.08.008

historical – possibly a decade or more ago) and an observed disease.

Recommendation

- It is advisable that workers with potential exposure to hepatotoxic chemicals receive a document listing the chemicals used in the factory. Such a document may be made available to the workers without request. **Grade D**
  Evidence: Level 5 (Expert opinion)

The National Institute for Occupational Safety and Health has published a pocket guide to hazardous chemicals.[64] This guide can help clinicians to know if the chemicals to which the patient has been exposed are known causes of the observed liver disease.

Host risk factors for occupational liver disease

Understanding what makes one particular worker susceptible to develop liver injury after exposure to industrial chemicals as opposed to other co-workers who do not manifest any hepatic dysfunction is key. The answer to this question is complex. Many industrial chemicals belong to the group of so called "intrinsic" hepatotoxins. These are substances with predictable toxicity, which dose-dependently and directly (or through activation of chemicals to toxic metabolites) produce liver damage. In practical terms, the dichotomy between intrinsic and idiosyncratic hepatotoxins is an overly simplified concept because the potential for toxic injury extends along a spectrum, modified by the toxin and host factors, involving different biochemical and immunological responses.[65] Elaborating on this concept, the hepatotoxic potential of some chemicals, such as phosphorus or pyrrolizidine alkaloids, is closely linked to the extent of exposure and rarely to host vulnerability. On the other hand, individual susceptibility is critical in determining the probability of developing liver injury from compounds such as halothane or paracetamol. Therefore, risk assessments should also take into account host-environmental interactions that will likely modulate the severity of liver injury and add complexity to the diagnosis of OLD.

Age and gender

Age plays an important role for drug disposition and sensitivity to xenobiotics. As body composition changes with age, particularly in women, exhibiting a higher percentage of adipose tissue, lipophilic chemicals could enhance the risk of liver injury.[66] However, the net effect of age as a risk modifier for OLDs is unknown.

In an experimental model, female rats exhibited a more severe phenotype of mercuric chloride-induced hepatotoxicity, as evidenced by higher increases in aminotransferases and histopathological findings.[67] Interestingly, in patients with DILI, despite an equal sex distribution, females are at a higher risk of developing acute liver failure.[68] Female sex might be a risk factor for chemical-induced liver injury, although robust evidence from human data is still lacking.

Drug-chemical interactions

Liver cytochrome P450 isozymes are responsible for the oxidative metabolism of most drugs and workplace-related xenobiotics. The concurrent administration of drugs and exposure to chemicals could either induce or inhibit microsomal activity, either directly or via the generation of reactive metabolites, thereby modifying the effect of either drug or chemical exposure. For instance, first-generation anti-epileptics are known for their enzyme inducing capacities. Hence, enzyme induction by carbamazepine, a known hepatotoxin in itself, favours chemically reactive metabolite formation from other chemicals, thereby increasing their risk of liver toxicity. This is exemplified by a carbamazepine-treated patient presenting with acute hepatitis resulting from the use of paints, paint thinner, carbon tetrachloride (CCl_4) and organic solvents in enclosed areas without ventilation, in whom the hepatotoxicity was mistakenly ascribed to carbamazepine.[69] The predisposition to severe liver and renal injury in a worker using CCl_4 to clean paintings, probably due to microsomal induction by concomitant treatment with phenobarbital, underscores the importance of not overlooking the potential for drug/xenobiotic interactions at the workplace.[70] In addition, we should also keep in mind the potential of xenobiotic interactions in industry workers exposed to multiple chemicals at once. Thus, a mixed exposure to chlorinated organic solvents, including dichloromethane, 1,2-dichloropropane, and trichloroethylene, may induce a synergistic effect towards the development of severe acute hepatitis.[71] Furthermore, in an experimental model, thinner pretreatment (methanol or toluene are the major constituents) via inhalation potentiated the hepatotoxicity induced by CCl_4 through an induction of microsome oxidases to increase the formation of free radicals and membrane lipid peroxidation.[72]

Recommendation

- Caregivers, as well as workers exposed to liver enzyme inducers and/or using enzyme inducing drugs should be informed of the possibility of interactions with anticonvulsant drugs. **Grade C**
  Evidence: Level 4 (case series)

Genetic variations in metabolic pathways

Genetic polymorphisms in genes encoding enzymes involved in xenobiotic metabolism (oxidation and detoxification) result in different drug levels, which can then result in variable drug effects, thus exemplifying another element that may determine an individual's susceptibility to chemical-induced liver disease. Hence, patients exhibiting a poor metaboliser genotype may show higher serum toxin concentrations and associated risk of toxicity. Hsiech *et al.*[73] showed in a longitudinal study of 320 workers exposed to VCM that 13 developed liver fibrosis with those that were homozygotes for CYP2E1 variant alleles (low activity) being overrepresented in this group. However, liver injury from drugs and chemicals is a complex process, reflecting the interplay between the toxin's physicochemical properties and host factors that modulate the final response to hazardous exposures.[74] Consequently, knowledge of genetic variability has not yet proven useful for discriminating high-risk populations.[75]

Please cite this article in press as: European Association for the Study of the Liver. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.08.008

Table 2. Overview of workplace-related toxicants and typical uses.

Toxicant	Uses (selection)
Arsenic	Pesticide; impurity in smelting processes
Carbon tetrachloride	Chemical manufacturing; cleaning fluid; dry cleaning; degreasing agent; refrigerant; pesticide
Chlordecone	Pesticide
Chlorinated hydrocarbons	Degreasers and cleaning solvent; refrigeration
Chloroform	Pharmaceutical industry; dyes and pesticides; reagent
1,4-Dichlorobenzene	Insecticide
Dimethylacetamide	Industrial solvent; production of acrylic fibers
Dimethylformamide	Industrial solvent, chemical manufacturing (acrylic fibers and plastic); paints
Dimethylnitrosamine	Waste product of rocket fuel manufacturing
Dioxin	Pesticide
Halothane	Anesthesiology
Hexachlorobenzene	Fungicide
Hydrazine	Rocket fuel; preparation of gas precursors in airbags; oxygen scavenger
Methylene dianiline	Production workers; intermediate for polyurethane foam insulation
2-Nitropropane	Paint; adhesive; coatings
Paraquat	Insecticide
Phosphorus	Munition
Polychlorinated biphenyls	Production; electrical utility (coolants, insulating fluids)
1,1,2,2-Tetrachloroethane	Aircraft manufacturing; formerly in paints and pesticides; dry cleaning; leather treatment
Toluene	Paints; coatings; adhesives; inks; cleaning agents; dyes
Trichloroethylene	Glue and cleaning solvent; grease remover; decaffeination of coffee
Trinitrotoluene	Munition
Vinyl chloride	Plastic (PVC) and rubber manufacturing
Xylene	Resins; gums; paints; adhesives; inks; gasoline

PVC, polyvinylchloride.

Indeed, according to the code of ethics issued by the International Commission on Occupational Health the selection of high-risk populations upon genetic testing should be considered unethical. Instead, improving working environments is recommended.[76]

Alcohol

There is agreement that social habits, such as alcohol consumption, can worsen or potentiate the toxicity associated with occupational exposure to chemical substances, thus acting as a confounding factor when making a diagnosis of the role of occupational exposure (*e.g.* fatty liver). Notably, the prevalence of alcohol use amongst industrial workers is inferred to be high, with reports of male workers having higher consumption than females.[77]

It is well recognised that alcohol consumption can increase the hepatotoxic effects of other compounds taken simultaneously through its inducing effect on the cytochrome P450 system (CYP), particularly the isoform CYP2E1.[78] Indeed, high alcohol intake had a severe potentiating effect on occupational exposure to CCl_4[79] and other chemicals that are activated by the same cytochrome P450 enzymes.[80] Alcohol drives the generation of toxic free radical intermediates and therefore enhances the likelihood of severe CCl_4-induced liver injury.[81]

Recommendation

- Caregivers and workers should be informed by the attending physician that alcohol can be toxic to the liver and potentiates liver toxicities due to occupational exposure. **Grade C**
  Evidence: Extrapolation from 2c studies (outcome research and mechanistic studies)

Pre-existing liver diseases

As exposure to some occupational toxins may induce acute or chronic liver injury, it is important to assess the functional status of patients' livers, as toxin exposure may be worsened by underlying liver disease. However, this remains quite a controversial issue, with minimal clinical data to support the view that underlying liver disease may increase susceptibility to occupational chemicals.[82]

Non-alcoholic fatty liver disease

NAFLD, the most prevalent liver disease worldwide, is considered the clinic-pathological hepatic manifestation of obesity and metabolic syndrome. It is recognised that in patients with NAFLD, CYP2E1 is upregulated (like in obese patients), favouring the metabolism of toxins (like VCM) into reactive metabolites, which could ultimately increase the susceptibility to toxicant-associated steatohepatitis (TASH) development. There is experimental evidence that exposure to low doses of VCM may also sensitise the liver to other metabolic stresses and potentiate liver injury.[83] Similarly, there is evidence that pre-existing NAFLD increases the risk of acetaminophen overdose-induced acute liver injury.[84] Notably, patients with NAFLD were not at a higher risk of statin hepatotoxicity.[85] However, a recent study in the US, using electronic medical records, showed that patients with surrogate markers of NAFLD (*i.e.* consistently elevated alanine aminotransferases [ALT] levels and high prevalence of hypertension, type II diabetes mellitus and obesity) had a greater incidence of suspected DILI related to the drugs most frequently involved in hepatotoxicity.[86] Interestingly, drugs inducing mitochondrial dysfunction such as tamoxifen, methotrexate and irinotecan can worsen steatohepatitis in patients with metabolic syndrome and obesity.[84,87] Thus, we could extrapolate from existing data that underlying NAFLD could increase susceptibility to TASH from industrial chemical exposure.[88]

Please cite this article in press as: European Association for the Study of the Liver. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.08.008

Recommendation

- Occupational workers with classical risk factors of fatty liver may be advised by the attending physician to have a baseline screen for NAFLD/ non-alcoholic steatohepatitis (NASH), alcohol-related fatty liver disease (AFLD)/ alcohol-related steatohepatitis (ASH), and a close follow-up. **Grade D**
  Evidence: Level 5 (Expert opinion)

Viral hepatitis

Nowadays, there are effective therapies for curing hepatitis C and for suppression of viraemia in patients with chronic hepatitis B. Hence, except in developing countries with limited access to these new therapies, chronic hepatitis B and C are not a concern for workers exposed to occupational chemicals. However, in patients with eradicated or controlled liver infection, residual lesions (fibrosis, steatosis) can persist. It is known that hepatitis C virus can be associated with a greater risk of diabetes, insulin resistance and consequently NAFLD. There is also a complex interplay between hepatitis B infection and NAFLD.[89] Furthermore, regression of fibrosis with long-term viraemia suppression in patients with chronic hepatitis B undergoing tenofovir therapy has been documented, with underlying NAFLD being suggested as an explanation for those who did not experience fibrosis regression.[90] Likewise, in patients exposed to occupational chemicals, regular alcohol intake above predefined thresholds (>20 g/day [women], >30 g/day [men]) should be investigated because it increases the risk of AFLD or ASH.[91]

Recommendation

- A screen for the concurrent presence of NAFLD/NASH, AFLD/ASH and/or residual fibrosis is suggested in workers with cured hepatitis C or controlled chronic hepatitis B virus infection and clinical data suggestive of NAFLD/ NASH, AFLD/ASH in order to better delineate their risk profile when exposed to chemicals. **Grade D**
  Evidence: Level 5 (Expert opinion)

Definition of liver injury in occupational liver diseases

Biochemical definition of acute liver injury

Hepatic injury in a working population exposed to potential hepatotoxins is generally detected by standard liver biochemistry that reflects necro-inflammatory processes in the liver.[92] These biomarkers are not specific for any form of toxic liver disease, lack mechanistic insight and may not confer prognostic significance.[93] The similar clinical and histopathological features of hepatic injury observed as a consequence of the exposure to occupational chemicals and drugs, makes it appropriate to adopt the consensus criteria used for DILI.[4,5] Using these criteria and by common convention, the thresholds of liver enzymes used to **define acute liver injury** are as follows (Table 3):

Table 3. Thresholds of liver enzymes used to define acute liver injury and pattern of damage according to Ratio (R) [4,5].

a. Any one of the following CRITERIA TO DEFINE LIVER INJURY*:
1) Alanine aminotransferase (ALT) level ≥5x upper limit of normality (ULN)
2) Alkaline phosphatase (ALP) level ≥2× ULN (particularly if concomitantly elevated gamma-glutamyl transpeptidase (GGT) in the absence of bone disease)
3) ALT level ≥3× ULN and simultaneous total bilirubin (TB) level >2× ULN
b. PATTERN OF LIVER INJURY according to R value:
R value is defined as: (ALT/ULN)/(ALP/ULN)***
Hepatocellular pattern: R ≥5
Cholestatic pattern: R ≤2
Mixed pattern: R value is >2 and <5

*In patients with abnormal baseline liver blood tests, ULN is replaced by the mean baseline values obtained prior to the exposure to the suspect chemical, and the increases in ALT, ALP and TB should be proportionate to this modified baseline.
***AST can replace ALT when this one is unavailable.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; ULN, upper limit of normal.

1) ALT level ≥5x the upper limit of normal (ULN)

2) Alkaline phosphatase (ALP) level ≥2× ULN (particularly if concomitantly elevated gamma-glutamyltransferase (GGT) in the absence of bone disease) or

3) ALT level ≥3× ULN and simultaneous total bilirubin (TB) level >2× ULN.

In patients with abnormal baseline liver blood tests, ULN is replaced by the mean baseline value obtained prior to exposure to the suspect chemical, and increases in ALT, ALP and TB should be proportionate to this modified baseline.

Isolated increases in GGT activity are not a marker of cellular damage, rather indicating enzyme induction. It is important to assess whether this liver parameter could be used in occupational medicine as a sensitive early indicator of biological change after exposure to toxicants, once alcohol consumption has been discarded as a causative factor.

The definitions used here refer to an acute hepatic reaction in people exposed to hepatotoxins; the difficulty remains how to define chronic liver disease induced by (transient exposure) to occupational chemicals.

Biochemical classification of drug-induced liver injury

The pattern of liver damage is classified according to International Consensus Meeting criteria,[4,5] which used ALT and ALP activity, expressed as a multiples of the ULN, to determine the ratio (R) of ALT/ALP. Aspartate aminotransferase (AST) can replace ALT when this one is unavailable.[94] Liver injury is termed hepatocellular when R ≥5, cholestatic when R ≤2, and mixed when R is >2 and <5. (Table 3). The values used for the classification of liver damage should be those available from blood tests when liver injury is first recognised. Due to the differences in the clearance kinetics of ALT and ALP, there is a tendency for the liver injury pattern to shift to a cholestatic/mixed biochemical signature.[68]

Alternatively, acute liver damage associated with occupational hepatotoxins can be classified based on liver biopsy findings, which can confirm the biochemical classification and also contribute to diagnostic accuracy. While in DILI the correlation

Please cite this article in press as: European Association for the Study of the Liver. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.08.008

between biochemical categorisation and the histological features is fair,[95] for OLDs, data on biochemical and histological correlation are lacking. Toxic exposure to drugs or chemicals can mimic virtually the entire spectrum of liver diseases, which applies especially for OLDs that can often present insidiously with atypical phenotypes of toxic liver injury, including steatosis, TASH, fibrosis, cirrhosis, vascular liver disorders and liver cancer.[88] In this context, the liver enzyme threshold values mentioned above are not applicable, because there is a poor relationship between the level of aminotransferases (that can even be normal) and the severity of the liver injury. Therefore, the definition of damage in the setting of a prolonged low-level exposure to occupational toxicants necessarily relies on imaging techniques and histopathological findings. Thus, the criteria adopted to define liver injury developed for DILI (mostly in an acute setting) may have a low sensitivity to detect chronic liver damage related to occupational exposure, which nonetheless can lead to significant liver disease in the long term.

Definition

Acute liver injury in occupational workers should be classified as hepatocellular, cholestatic and mixed, according to liver biochemistry during the first laboratory assessment at recognition.

Evidence: Level 5 (expert opinion)

Grading severity of chemical-induced liver disease

An attempt to grade the severity of OLDs in a comprehensive and systematic way has not proven possible due to the lack of robust evidence. The standard classification used to grade idiosyncratic drug-induced acute liver failure may not apply when considering occupational liver injury because of the direct, massive and rapid liver damage induced by the chemical alongside the often simultaneous involvement of other organs.[96] Hence, the characteristic delay of 26 weeks between the onset of jaundice and the appearance of encephalopathy, which is typical for idiosyncratic drug-induced acute liver failure, will likely not occur. On the contrary, fulminant liver failure with symptoms appearing 24–48 h after exposure to the chemical, as observed with CCl_4 poisoning, may be the standard for acute exposure to occupational toxicants.[97]

In OLD, other organ failures may be the consequence of the direct effect of the chemical but may also arise from multi-organ failure in the setting of severe liver damage. Indeed, only for a few selected chemicals does hepatotoxicity dominate the clinical picture. These include VCM,[13] methylene dianiline,[98] and dimethylformamide (DMF), the universal solvent.[99] Taking into account these limitations, the severity of chemical liver injury may be evaluated using the adapted severity index scale for DILI (Table 4) (adapted from [4] and [5])].

Recommendation

- Severity of acute chemical liver injury can be evaluated using the adapted severity index scale designed for DILI.
  Grade D
  Evidence: Level 5 (expert opinion)

Clinical-pathological presentations

OLD may present with a wide spectrum of histological lesions ranging from hepatocellular, mixed hepatocellular/cholestatic, vascular, TASH, fibrosis, and malignancy, some of which may coexist in the same patient. Importantly, there are no morphological features that are pathognomonic of toxic injury.

OLD results from high accidental exposure or from prolonged low-level exposures. The former is relatively uncommon and is easily recognised clinically, whereas the latter is more frequent but often overlooked because of the insidious onset, asymptomatic nature, confounding by concurrent conditions and because liver biochemistry may be unremarkable. In addition, specific tests of toxicity are not available, histopathology may not be revealing and the assessment of internal dosing of chemicals is almost always not decisive. Consequently, the long-term effects of low-level exposure on chronic liver disease and liver cancer remain a concern.

On the other hand, whereas there is no evidence to suggest that a transient exposure to occupational chemical hepatotoxins may lead to a chronic liver disease, it might occur, as has been the case for very specific drugs. Indeed, short term use of ebrotidine, an H2 receptor antagonist withdrawn from the market in Spain because of hepatotoxicity, led to cirrhosis rapidly after initial presentation with acute hepatocellular injury.[100] Interestingly, ebrotidine has in its chemical structure a bromobenzene ring[101] and the brominated benzenes have been related to hepatotoxicity in experimental studies.[102]

Given these circumstances a classification according to clinical presentation is more appropriate.

Table 4. Category severity description[#].

1. Grade mild:	Elevated alanine aminotransferase/ alkaline phosphatase (ALT/ALP) concentration reaching criteria for liver injury* but bilirubin concentration <2 upper limit of normality (ULN)
2. Grade moderate:	Elevated ALT/ALP concentration reaching criteria* for liver injury and bilirubin concentration ≥2× ULN, or symptomatic hepatitis
3. Grade severe:	Elevated ALT/ALP concentration reaching criteria for liver injury, bilirubin concentration ≥2× ULN, and one of the following: • International normalized ratio ≥1.5 • Ascites and/or encephalopathy, and absence of underlying cirrhosis • Other organ failure considered to be due to occupational liver injury or to the toxic exposure
4. Grade fatal or liver transplantation:	Death or transplantation due to liver injury

[#]Category adapted from references 4 and 5.
*Criteria for liver injury are defined in Table 3.
The international normalized ratio (INR) or standardized prothrombin time.

Please cite this article in press as: European Association for the Study of the Liver. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.08.008

Acute liver injury

Acute hepatitis due to extensive exposure to a toxic agent may result from inhalation (the most important portal of entry), percutaneous absorption or accidental ingestion.

Hepatocellular necrosis

Almost all forms of acute environmental hepatic injury in humans involve the hepatic parenchyma and produce hepatocellular jaundice. Hepatocyte cytotoxicity and the resulting hepatocellular necrosis characterise most of these acute effects, though in some cases histopathological findings show peculiar features (Table 1). In some instances, hepatocellular damage may present with accompanying hypersensitivity features. Indeed, hepatitis associated with generalised skin disorders has been reported in workers from China and Asia who have been exposed to TCE.[103] Inclusions of copper in lungs and liver were detected in vineyard sprayers[104] and liver histology showed diffuse proliferation of Kupffer cells, sarcoid-like granulomas and atypical proliferation of sinusoidal lining cells. However, it should be noted that acute hepatic injury in the setting of systemic toxicity can be overlooked, as the liver injury may be less significant, in comparison to prominent extrahepatic clinical manifestations of toxicity such as renal failure, skin or pulmonary toxicity.[105]

Acute cholestasis/mixed injury

Hepatocellular necrosis with cholestatic lesions is produced by methylenedianiline[98] and the toxic herbicide paraquat.[106]

Microvesicular steatosis

Microvacuolar steatosis, characterised by the presence of foamy changes in the hepatocyte cytoplasm which is composed of tiny fat droplets with a preserved centrally located nucleus, has been reported upon exposure to dimethylformamide.[107]

Chronic liver injury

Toxicant-associated steatohepatitis

Fatty liver has been related to the occupational exposure to organic solvents.[108,109] TASH has been described in highly exposed VCM workers.[110] It is a severe form of fatty liver characterised by steatosis, inflammatory infiltrates, ballooning hepatocytes and in some cases fibrosis and cirrhosis, and then is pathologically indistinguishable from NASH even occurring in lean individuals.[111] Some patients exposed to industrial chemicals do not have the traditional risk factors of NASH and the conventional markers of liver damage may be normal.[88] Indeed, fibrosis was reported in as many as 55% of highly exposed VCM workers showing TASH, while serum aminotransferases were within normal ranges in most cases.[110]

Brazilian petrochemical workers were more likely to develop abnormal aminotransferases and GGT values than those in the administrative part of the industry, even after controlling for alcohol consumption, obesity and history of hepatitis.[112] Interestingly, 72% of the petrochemical workers with a diagnosis of NAFLD did not have insulin resistance suggesting that exposure to these volatile substances can itself induce accumulation of fat in the liver.[113] Indeed, abnormal liver enzymes and histology typically subsided in these patients when they were moved away from the industrial area.[114] Furthermore, individuals exposed to volatile chemicals (benzene, xylene, VCM, and others) with abnormal liver tests and without evidence of obesity or other features of metabolic syndrome at presentation had a distinctive profile: they were younger men and more frequently developed steatosis, fibrosis and cholestasis in liver biopsies.[115]

Fibrosis

Fibrosis may accumulate in the liver because of chronic insults induced by various toxicants through the development of chronic hepatitis, subacute necrosis or steatohepatitis injury. While periportal fibrosis has been clearly associated with long-term exposure to VCM, progression to cirrhosis has been discussed much more.[116,117] An excess of deaths from non-alcohol related cirrhosis has been observed among female rubber workers, suggested to be associated with occupational exposure to nitrosamines.[118]

Vascular disorders

A number of vascular lesions may be produced by toxicants. These include:

Sinusoidal obstruction syndrome. Sinusoidal obstruction syndrome (SOS) is associated with endothelial injury in the sinusoids, predominantly in the centrolobular areas, resulting in sinusoidal dilatation, congestion with hepatocyte atrophy, and potentially obliterative oedema to fibrotic changes of small hepatic veins (so called veno-occlusive disease).[119] Clinical presentation may depend on the extent of liver injury from mild liver test abnormalities to abdominal swelling and pain, ascites, hepatomegaly and splenomegaly.[120]

Peliosis. Peliosis, defined by large blood-filled cavities not lined by endothelial cells, results from damage to sinusoidal cells. Marked sinusoidal dilatation is often concomitantly observed.[121]

Porto-sinusoidal vascular disease (previously known as hepatoportal sclerosis). Porto-sinusoidal vascular disease, a cause of "idiopathic/non-cirrhotic portal hypertension", is characterised by portal vein obliteration associated with progressive periportal fibrosis.[122] It can result from long exposure to VCM and in vineyards to sprays containing copper sulphate and lime.[123] It seems to be a precursor lesion of angiosarcoma.[124]

Liver malignancies

Primary liver malignancies may develop from epithelial (HCC or biliary/cholangiocarcinoma) or mesenchymal (endothelial/angiosarcoma, vascular/leiomyosarcoma) cells). The most recognised association between toxicants and primary liver malignancies is VCM and angiosarcoma.

Angiosarcoma. Angiosarcomas are high grade tumours that grow rapidly and may lead to hepatomegaly and jaundice. Indeed, angiosarcoma has a very poor prognosis as it is diagnosed at a symptomatic phase, advanced and not resectable or transplantable. At macroscopy, angiosarcomas are often large haemorrhagic nodules, ill-defined, with variably solid and cystic areas. Histologically, the tumour is highly cellular and composed of atypical endothelial cells, elongated or with epithelioid appearance. Different growth patterns may be observed: sinusoidal, solid, papillary, cavernous and anastomosing types. Invasion of hepatic or portal veins is frequent. Specific genomic alterations are observed, including amplification of genes *MYC* and *FLT4*.[125,126]

Please cite this article in press as: European Association for the Study of the Liver. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.08.008

Epithelioid haemangioendothelioma. Epithelioid haemangioendothelioma (EHE) of the liver is a recently recognised and uncommon neoplasm of vascular origin. Gelin *et al.*, described the first case occurring after close contact with VCM. The patient developed serious portal hypertension with bleeding varices, which required liver transplantation. The patient died 20 months later from variceal haemorrhage and encephalopathy due to local tumour recurrence with portal thrombosis.[127]

Hepatocellular carcinoma. HCC developed in the setting of OLD does not present any specific morphological features. A distinct case of sequential occurrences of HCC and angiosarcoma of the liver was recently reported in a VCM-exposed worker without cirrhosis and any known risk factor for chronic liver disease.[128] Besides, a *KRAS* G12D point mutation, which is considered to be characteristic of VCM-induced angiosarcoma, was present. Back in 1983, Evans *et al.* also identified concurrent and sequential angiosarcoma and HCC in 5 VCM workers.[129]

Diagnosis

Diagnosis relies on a high level of suspicion. A stepwise algorithm approach to OLD diagnosis is depicted in Fig. 1. Thus, in order to establish causality, a coherent synthesis is required between the characteristics of the patient's disease (phenotype), the exclusion of more common liver disorders, the collection of a thorough occupational history, the presence of hepatotoxic chemicals within an industrial process and their known capability to cause that disease along with the intensity and length of exposures experienced by the workers.

The report of 3 different recurrent acute liver injury episodes, occurring after inadvertent re-exposure to organic solvents at work, highlights the importance of considering OLDs despite their rarity in the differential diagnosis of toxic hepatitis, in order to reach an accurate diagnosis.[130]

In the EU, the diagnosis of OLD, as well as any other occupational disease, relies heavily upon the expertise of certified occupational physicians, those professionals who are responsible for the health surveillance of workers. All workers exposed to (hepatotoxic) chemicals in the EU should follow preventive measures and undergo periodical medical surveillance by a designated occupational physician. His/her tasks include the assessment of chemical exposure by environmental and/or biological monitoring, workplace visits, information to the workers and other preventive measures. Therefore, the occupational physician has a key role (and responsibility) in putting together the specific clinical and exposure information available to other professionals involved in the prevention, detection and management of OLD and interpreting the evidence provided by the rest of the team.

Recommendation

- The diagnosis of OLD should rely on the judgment of an expert occupational physician. The assessment of OLD may be improved, on a case by case basis, by input from a multidisciplinary team including hepatologists, pathologists, toxicologists, and epidemiologists. **Grade D**
  Evidence: Level 5 (expert opinion)

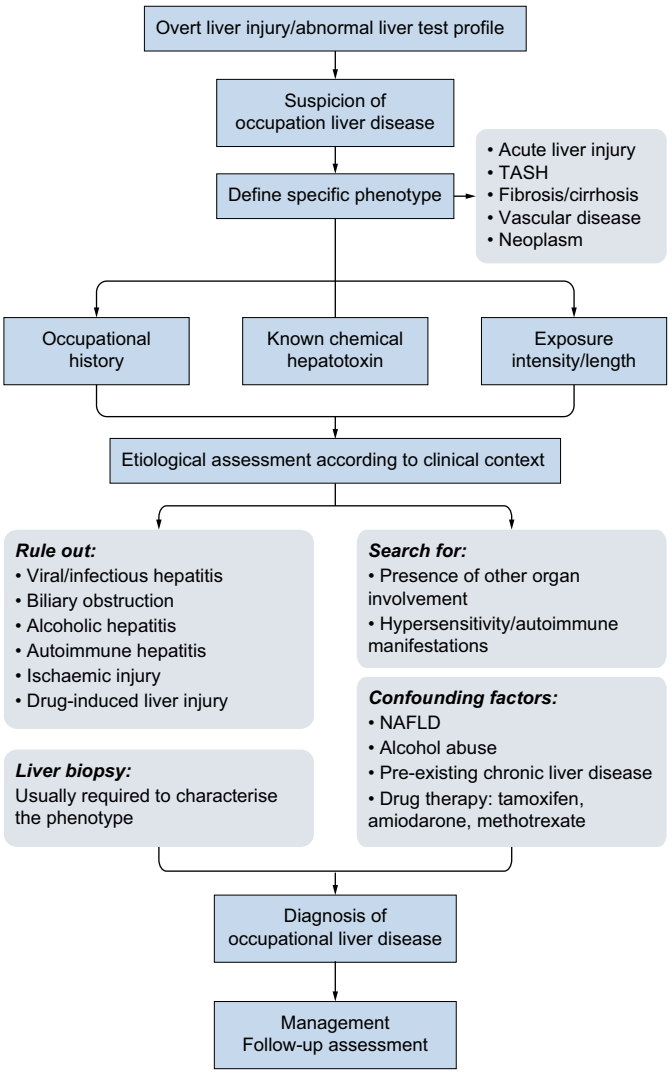

Fig. 1. Schematic approach to the assessment and diagnosis of occupational liver disease. OLD, occupational liver diseases; TASH, toxicant-associated steatohepatitis.

Collecting the occupational history

OLDs very rarely display pathognomonic signs and, because of the multifactorial causality of disease, the physician should try to assess the relevance of occupational components in an all-encompassing approach. Taking an occupational history represents a key step in the clinical assessment of suspected OLD. Thus, in addition to focusing on the patient's symptoms, the work environment must be explored, bearing in mind that occupational exposure occurs most commonly by inhalation and through the skin. The list of information to be obtained from the patient/worker is detailed in Box 2.

In conclusion, collecting all relevant information about the occupation and associated environment is challenging and often requires a multidisciplinary approach that involves occupational medicine physicians and industrial hygienists. The expertise of toxicologists and epidemiologists may also be needed, given the discrepancy between a large number of chemicals that cause liver toxicity experimentally, with little or no evidence in humans[131] (Box 3).

Please cite this article in press as: European Association for the Study of the Liver. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.08.008

Box 2. Critical information to be obtained from the patient with a suspicion of occupational liver disease.

1. A chronological summary of all work activities and their duration.
2. A detailed description of the work place, of the job and of a typical working day.
3. An inventory of all chemicals that are present and how are used. Sometimes this information can be obtained from the managment.
4. Details of any measures to limit chemical exposure such as: work place ventilation and the nature protective measures that are taken (requirement to wear special clothing and gloves, the use of masks, goggles and other devices).
5. Enquiring if programs of industrial hygiene, biological monitoring and medical surveillance are or have been in place and retrive the result, if necessary, keeping in mind however that compliance with occupational exposure limits do not necessarily protect all workers from adverse effects.
6. Enquire as to whether coworkers have similar symptoms and signs to those of a patient with suspected occupational liver disease. This may involve questioning and even examining coworkers. If several cases come to light, it may be possible to demonstrate an exposure-response relationship.
7. Enquire if compensation procedures have been undertaken and results are available.
8. Exposures to chemicals other than those present at work places, associated for instance with environmental air pollution, hobbies, recreational habits and others should be ruled out.

Box 3. The assessment of occupational liver disease may be improved, on a case by case basis, by input from a multidisciplinary team encompassing.

- Occupational physicians
- Hepatologists
- Pathologists
- Toxicologists
- Epidemiologists

Assessment of exposure

An inherent difficulty when assessing exposure to chemicals is the unequivocal demonstration of this exposure. As outlined before, liver injury markers such as ALT, AST and GGT or, more recently, miRNAs, merely represent liver damage and, although they may be used for classification of the type of liver damage, they do not offer any insight into the aetiology underlying this damage.[132] In essence, there are no long-term biomarkers that can lead to identification of historical exposure (*i.e.* exposure that took place (many) years ago) to a potential hazardous chemical. Exposure data may, however, be available and be consulted retrospectively. Monitoring systems at the workplace is one way to deduce exposure data. These data could be used to consult workplace exposure limit databases, such as those from National lists of occupational limit values (OEL) from EU member states, including Germany (DFG-MAK Commission), The Netherlands (DECOS), and France (ANSES), and also from other sources such as the Scientific Committee on Occupational Exposure Limits (SCOEL),[133] the Occupational Safety and Health Administration (OSHA), the National Institute of Safety and Health (NIOSH) or the American Conference of Governmental Industrial Hygienists (ACGIH). Also, data from biomonitoring may be available. Such data are superior to those obtained from workplace monitoring systems, as they allow a personalised view of the exposure. Moreover, in instances where the exposure is relatively recent (during the past months) or still ongoing, biomonitoring could be applied to objectively document the exposure and, based upon quantitative assessments, even make statements about the extent of exposure.

Urine and blood are the most commonly used biological matrices for biomonitoring. However, for both matrices, the window of detection of the toxicants themselves or their metabolites is quite limited (typically maximally in the range of days). For a more extended historical window, segmental hair analysis could be used or, alternatively, adducts in blood could be monitored.[134,135] Many of the toxicants listed in Table 1 will be converted to reactive intermediates in the liver, which will form covalent adducts with macromolecules such as DNA and proteins. As both haemoglobin and albumin are highly abundant proteins, many groups have focused on adducts with these proteins to document exposure to toxicants, even when these toxicants or their metabolites are no longer detectable in blood or urine. Adducts with haemoglobin are detectable up to >100 days following exposure, as their disappearance is linked to the lifespan of red blood cells, which is about 4 months. When the timing of the exposure is known, it is even possible to perform a back-calculation to derive the adduct concentration right after the exposure took place (in case of acute exposure). This gives an idea about the extent of exposure, compared to the background exposure, typically assessed in a reference population.[136] Yet, it should be remarked that there is not necessarily a link between the level of exposure and the extent of damage, as this will be compound dependent. Although the markers that can be assessed this way are highly selective, there are still confounding factors. For example, smoking results in elevated levels of several albumin and haemoglobin adducts, rendering it impossible to distinguish moderate exposure to certain toxicants from the contribution by smoking.[137,138] Although adduct monitoring has already successfully been applied for a number of compounds listed in Table 1, this approach has not yet been widely applied for assessing (the absence or extent of) occupational exposure.[135,137,139,140] The occupational history and, when available, the result of workplace monitoring and biomonitoring, are crucial for formulating a presumptive diagnosis. It is occasionally necessary to remove the patient from exposure to the suspected workplace toxic substance to establish the workplace relationship.

Workup for alternative aetiologies

Laboratory tests

A comprehensive liver aetiology screen should be undertaken, including evaluation of viral serology (hepatitis A-E), liver autoantibodies and serum immunoglobulins, ferritin and transferrin saturation, alpha-1-anti-trypsin levels and ceruloplasmin (depending on age).

Please cite this article in press as: European Association for the Study of the Liver. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.08.008

Imaging
Imaging investigations will be determined by the clinical presentation and nature of likely toxin exposure. In many instances, patients will have an initial abdominal ultrasound but may require additional computed tomography (CT) or magnetic resonance imaging (MRI) scanning to delineate the nature of lesions and examine the biliary system in more detail. Indeed, routine abdominal ultrasound along with evaluation of liver fibrosis using transient elastography are advisable in all cases.

Non-invasive diagnosis of liver disease
Non-invasive markers like transient elastography, Fib-4 (Fibrosis 4) and albumin to platelet ratio index (APRI) have been applied to identify and stage liver diseases across multiple aetiologies.[141] In the setting of liver injury associated with occupational exposure, these tests might help i) Identify sub-clinical hepatic injury not accompanied by symptoms and/or abnormalities of serum liver blood tests, ii) Stage the severity of overt chronic liver disease and, iii) Evaluate resolution of acute liver injury, chronicity suspected after 12 months of persistent alteration (as in DILI[4]). Whilst the majority of non-invasive tests were conceived as markers of liver fibrosis, increasingly there are data to suggest they may provide information on necroinfammation and degeneration of liver cells.[141]

While workers exposed to toxicants may develop a variety of histopathological lesions in the liver, TASH mimics histopathological changes observed in NASH. This is a major challenge, as NASH is emerging as an epidemic across all age strata worldwide, therefore making the characterisation of TASH extremely difficult.[110,115] Indeed, an individual with liver disease must be removed from exposure, however this does not necessarily provide evidence of a relationship with work environment.

Recommendation

- Staging of OLD can require dynamic evaluation with repeat measurements of liver tests and liver stiffness by transient elastography or serum predictors of fibrosis like Fib-4 and APRI after patient removal from occupational exposure to suspected toxicants. **Grade D**
  Evidence: Level 5 (Expert Opinion)

Liver biopsy
Liver biopsy is currently the most reliable approach for diagnosis and staging of liver disease of any aetiology, but it is limited by cost, sampling error and procedure-related morbidity and mortality. In patients with more than 1 risk factor, liver biopsy remains the most robust diagnostic approach to define the cause of underlying liver abnormalities. Workers exposed to potentially hepatotoxic agents may in fact present with comorbidities like overweight, diabetes, arterial hypertension, alcohol abuse, viral hepatitis and medications that cause persistence of liver abnormalities after withdrawal from occupational exposure and may require histological examination of the liver for a definite diagnosis.

When performing a liver biopsy to diagnose a liver mass, sampling of non-tumoral liver is advisable to assess the status of the background liver.

Recommendations

- Liver biopsy may be performed in patients with persistently abnormal non-invasive liver tests, depending on the clinical context and the magnitude of the liver abnormalities. **Grade D**
  Evidence: Level 5 (Expert Opinion)
- When performing a liver biopsy to diagnose a liver mass, sampling of non-tumoral liver is suggested. **Grade D**
  Evidence: Level 5 (Expert Opinion)

Follow-up
For episodes of acute liver injury with no evidence of liver fibrosis, patients should be followed-up until there is complete resolution of any abnormal liver parameters.

For patients with persistent alterations in liver tests after removal from exposure, one should search for confounding factors or alternative aetiologies and stratify follow-up accordingly to the presence of these coexisting disorders.

Management

Patient management will largely be determined by the nature and severity of the OLD. In acute injury cases the priority is to remove the patient from further exposure whilst establishing the level of liver dysfunction. In the event that the acute liver dysfunction is severe and ongoing, consideration should be given to the appropriate setting within the hospital and need for liver transplantation. This will be determined by the magnitude of liver dysfunction using internationally accepted criteria.[142]

In the setting of chronic disease, the degree of liver fibrosis will determine management. Advanced fibrosis/cirrhosis will prompt evaluation for the complications of chronic liver disease and also transplantation if there is evidence of significant decompensation.[142]

There is a need to inform the competent health authority/-compensation agency.

Recommendation

- The relevant health authority and/or compensation agency can be informed of the documented or suspected OLD case. **Grade D**
  Evidence: Level 5 (Expert Opinion)

Prevention

Successful prevention has markedly reduced the risk of liver diseases to workers, although areas of high risk still exist, particularly in developing countries. Two broad approaches to prevent workers from being affected by liver toxicants are used; primary prevention involves either elimination or control of exposures through interventions in the working environments and secondary prevention is aimed at the

Please cite this article in press as: European Association for the Study of the Liver. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.08.008

identification of excessive exposure and early clinical effects in individuals. Thus, prevention is achieved with industrial hygiene techniques, mainly with adherence to exposure limits, and programmes of medical surveillance of exposed workers, aimed at avoiding further damage by removing workers from additional exposure. The decision to temporally or permanently remove the affected workers from the workplace depends on the severity of OLD, working environment and social factors.

As mentioned earlier (section 7.b), the occupational risk is assessed by comparing the measurement of a given environmental exposure with an appropriate exposure limit. These limits may refer to the risk of inhalation or dermal exposures, or both, depending on the chemicals and their uses, and are intended to protect the majority of exposed workers. However, a number of variables influence the exposure of a single worker in addition to a given environmental concentration, including the way materials are handled, the size and ventilation of a specific workplace and the amount of time spent doing specific tasks. Thus, in order to have a reliable assessment of exposure, several environmental measurements are usually needed. While most countries have their own exposure limits, these are broadly comparable with the American ACGIH-derived threshold limit values,[143] which are revised on a regular basis, being the most influential worldwide.

In some circumstances environmental exposures can be controlled at an individual level through the use of biological monitoring as part of medical surveillance.[144,145] This is based on the analysis of substances or their metabolites in biological fluids, usually blood, urine or breath, which reflects systemic exposures and may provide feedback to ensure the accuracy of environmental assessments. For certain substances biological limit values have also been suggested. Biological monitoring of exposures to hepatotoxic chemicals also includes the assessment of possible consequences by utilising the panel of liver blood tests routinely used in clinical diagnosis. However, these conventional markers may be normal, even in the presence of liver damage and specific tests of toxicity are not available. Raising worker awareness about risks through the provision of information, instruction and training is one of the most important and effective aspects of prevention.

Unmet needs and future research

A step forward in improving safety in the workplace is collecting cohort data from occupational registries including clinical, biochemical and follow-up information in order to obtain incidence figures of hepatotoxicity and trends in (re)-emerging OLD. The importance of reporting associations between environmental exposure and possible liver disease outside registries should also be highlighted.

Another unmet need is the development and quantification of sensitive and specific biomarkers of liver damage caused by toxicants that may help in fine-tuning the differential diagnosis, without the need for histological examination of the liver, and could provide prognostic clues. Advances in the field of biomarkers would allow more effective risk stratification algorithms, while providing mechanistic insights that would help in the development of safe and effective treatments.

Conflict of interest

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

Acknowledgements

We would like to thank the reviewers of this Clinical Practice Guideline for their time and critical reviewing: EASL Governing Board, Jordi Bruix and Maurizio Manno.

We thank Professor Laurent Castera, Hospital Beaujon, Clichy, France for his thoughtful insights in non-invasive diagnosis of liver damage and Professor Raul J Andrade, Hospital Universitario Virgen de la Victoria, IBIMA, UMA, Malaga, Spain, CIBERehd, for his suggestions and recommendations in chemical-induced liver injury definition, severity, risk factors and assessment. We acknowledge the support from European Cooperation in Science & Technology (COST) Action CA17112 Prospective European Drug-Induced Liver Injury Network. MIL and RJA are members of COST Action CA17112.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.08.008.

References

Author names in bold designate shared co-first authorship

[1] Guarnieri G, Bizzotto R, Gottardo O, Velo E, Cassaro M, Vio S, et al. Multiorgan accelerated silicosis misdiagnosed as sarcoidosis in two workers exposed to quartz conglomerate dust. Occup Environ Med 2019;76:178–180.
[2] Deng H, Eckel SP, Liu L, Lurmann FW, Cockburn MG, Gilliland FD. Particulate matter air pollution and liver cancer survival. Int J Cancer 2017;141:744–749.
[3] Pan W-C, Wu C-D, Chen M-J, Huang Y-T, Chen C-J, Su H-J, et al. Fine particle pollution, alanine transaminase, and liver cancer: a taiwanese prospective cohort study (REVEAL-HBV). J Natl Cancer Inst 2015;108.
[4] EASL. Clinical Practice Guidelines: drug-induced liver injury. J Hepatol 2019;70:1222–1261.
[5] Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther 2011;89:806–815.
[6] Oxford Centre for Evidence-Based Medicine – Levels of evidence (March 2009) – CEBM 2009. Available at: https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/ (accessed February 23, 2018).
[7] Cornberg M, Tacke F, Karlsen TH. European Association for the Study of the Liver. Clinical Practice Guidelines of the European Association for the Study of the Liver – advancing methodology but preserving practicability. J Hepatol 2019;70:5–7.
[8] Chen F-L, Chen PY. Health disparities among occupations in Taiwan: a population study. J Occup Health 2012;54:147–153.
[9] Lee H-E, Kim H-R, Chung YK, Kang S-K, Kim E-A. Mortality rates by occupation in Korea: a nationwide, 13-year follow-up study. Occup Environ Med 2016;73:329–335.
[10] Leigh JP, Jiang WY. Liver cirrhosis deaths within occupations and industries in the California occupational mortality study. Addiction 1993;88:767–779.
[11] Coggon D, Harris EC, Brown T, Rice S, Palmer KT. Occupation and mortality related to alcohol, drugs and sexual habits. Occup Med (Lond) 2010;60:348–353.
[12] Ward E, Boffetta P, Andersen A, Colin D, Comba P, Deddens JA, et al. Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry. Epidemiology 2001;12:710–718.

Please cite this article in press as: European Association for the Study of the Liver. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.08.008

[13] Mundt KA, Dell LD, Crawford L, Gallagher AE. Quantitative estimated exposure to vinyl chloride and risk of angiosarcoma of the liver and hepatocellular cancer in the US industry-wide vinyl chloride cohort: mortality update through 2013. Occup Environ Med 2017;74:709–716.
[14] Frullanti E, La Vecchia C, Boffetta P, Zocchetti C. Vinyl chloride exposure and cirrhosis: a systematic review and meta-analysis. Dig Liver Dis 2012;44:775–779.
[15] Lotti M. Do occupational exposures to vinyl chloride cause hepatocellular carcinoma and cirrhosis? Liver Int 2017;37:630–633.
[16] Lester D, Greenberg LA, Adams WR. Effects of single and repeated exposures of humans and rats to vinyl chloride. Am Ind Hyg Assoc J 1963;24:265–275.
[17] Wiśniewska-Knypl JM, Klimczak J, Kołakowski J. Monooxygenase activity and ultrastructural changes of liver in the course of chronic exposure of rats to vinyl chloride. Int Arch Occup Environ Health 1980;46:241–249.
[18] Falk H, Creech JL, Heath CW, Johnson MN, Key MM. Hepatic disease among workers at a vinyl chloride polymerization plant. JAMA 1974;230:59–63.
[19] Thomas LB, Popper H, Berk PD, Selikoff I, Falk H. Vinyl-chloride-induced liver disease from idiopathic portal hypertension (Banti's syndrome) to angiosarcomas. N Engl J Med 1975;292:17–22.
[20] Anisimov VN, Baturin DA, Popovich IG, Zabezhinski MA, Manton KG, Semenchenko AV, et al. Effect of exposure to light-at-night on life span and spontaneous carcinogenesis in female CBA mice. Int J Cancer 2004;111:475–479.
[21] Kettner NM, Voicu H, Finegold MJ, Coarfa C, Sreekumar A, Putluri N, et al. Circadian homeostasis of liver metabolism suppresses hepatocarcinogenesis. Cancer Cell 2016;30:909–924.
[22] Balakrishnan M, El-Serag HB, Kanwal F, Thrift AP. Shiftwork is not associated with increased risk of NAFLD: findings from the national health and nutrition examination survey. Dig Dis Sci 2017;62:526–533.
[23] Creech JL, Johnson MN. Angiosarcoma of liver in the manufacture of polyvinyl chloride. J Occup Med 1974;16:150–151.
[24] Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. IARC Monogr Eval Carcinog Risks Hum 1987;7:1–440.
[25] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Chemical agents and related occupations. IARC Monogr Eval Carcinog Risks Hum 2012;100:9–562.
[26] Boffetta P, Matisane L, Mundt KA, Dell LD. Meta-analysis of studies of occupational exposure to vinyl chloride in relation to cancer mortality. Scand J Work Environ Health 2003;29:220–229.
[27] Bosetti C, La Vecchia C, Lipworth L, McLaughlin JK. Occupational exposure to vinyl chloride and cancer risk: a review of the epidemiologic literature. Eur J Cancer Prev 2003;12:427–430.
[28] Cicalese L, Raun L, Shirafkan A, Campos L, Zorzi D, Montalbano M, et al. An ecological study of the association between air pollution and hepatocellular carcinoma incidence in Texas. Liver Cancer 2017;6:287–296.
[29] Jollow DJ, Bruckner JV, McMillan DC, Fisher JW, Hoel DG, Mohr LC. Trichloroethylene risk assessment: a review and commentary. Crit Rev Toxicol 2009;39:782–797.
[30] Rusyn I, Chiu WA, Lash LH, Kromhout H, Hansen J, Guyton KZ. Trichloroethylene: mechanistic, epidemiologic and other supporting evidence of carcinogenic hazard. Pharmacol Ther 2014;141:55–68.
[31] Scott CS, Jinot J. Trichloroethylene and cancer: systematic and quantitative review of epidemiologic evidence for identifying hazards. Int J Environ Res Public Health 2011;8:4238–4272.
[32] Alexander DD, Kelsh MA, Mink PJ, Mandel JH, Basu R, Weingart M. A meta-analysis of occupational trichloroethylene exposure and liver cancer. Int Arch Occup Environ Health 2007;81:127–143.
[33] Lynge E, Andersen A, Rylander L, Tinnerberg H, Lindbohm M-L, Pukkala E, et al. Cancer in persons working in dry cleaning in the Nordic countries. Environ Health Perspect 2006;114:213–219.
[34] Blair A, Petralia SA, Stewart PA. Extended mortality follow-up of a cohort of dry cleaners. Ann Epidemiol 2003;13:50–56.
[35] Vlaanderen J, Straif K, Pukkala E, Kauppinen T, Kyyrönen P, Martinsen JI, et al. Occupational exposure to trichloroethylene and perchloroethylene and the risk of lymphoma, liver, and kidney cancer in four Nordic countries. Occup Environ Med 2013;70:393–401.
[36] EPA U.S. (U.S. Environmental Protection Agency). Tetrachloroethylene (Perchloroethylene) (CASRN: 127-18-4) 2012:1–1077. Available at: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0106tr.pdf (accessed September 7, 2018).
[37] Bosetti C, Negri E, Fattore E, La Vecchia C. Occupational exposure to polychlorinated biphenyls and cancer risk. Eur J Cancer Prev 2003;12:251–255.
[38] Mallin K, McCann K, D'Aloisio A, Freels S, Piorkowski J, Dimos J, et al. Cohort mortality study of capacitor manufacturing workers, 1944–2000. J Occup Environ Med 2004;46:565–576.
[39] Pesatori AC, Grillo P, Consonni D, Caironi M, Sampietro G, Olivari L, et al. Update of the mortality study of workers exposed to polychlorinated biphenyls (Pcbs) in two Italian capacitor manufacturing plants. Med Lav 2013;104:107–114.
[40] Ruder AM, Hein MJ, Nilsen N, Waters MA, Laber P, Davis-King K, et al. Mortality among workers exposed to polychlorinated biphenyls (PCBs) in an electrical capacitor manufacturing plant in Indiana: an update. Environ Health Perspect 2006;114:18–23.
[41] Prince MM, Ruder AM, Hein MJ, Waters MA, Whelan EA, Nilsen N, et al. Mortality and exposure response among 14,458 electrical capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Environ Health Perspect 2006;114:1508–1514.
[42] Ruder AM, Hein MJ, Hopf NB, Waters MA. Mortality among 24,865 workers exposed to polychlorinated biphenyls (PCBs) in three electrical capacitor manufacturing plants: a ten-year update. Int J Hyg Environ Health 2014;217:176–187.
[43] Lauby-Secretan B, Loomis D, Grosse Y, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, et al. Carcinogenicity of polychlorinated biphenyls and polybrominated biphenyls. Lancet Oncol 2013;14:287–288.
[44] Silver SR, Bertke SJ, Hines CJ, Alavanja MCR, Hoppin JA, Lubin JH, et al. Cancer incidence and metolachlor use in the agricultural health study: an update. Int J Cancer 2015;137:2630–2643.
[45] Hernández AF, Amparo Gómez M, Pérez V, García-Lario JV, Pena G, Gil F, et al. Influence of exposure to pesticides on serum components and enzyme activities of cytotoxicity among intensive agriculture farmers. Environ Res 2006;102:70–76.
[46] Hernández AF, Gil F, Lacasaña M, Rodríguez-Barranco M, Tsatsakis AM, Requena M, et al. Pesticide exposure and genetic variation in xenobiotic-metabolizing enzymes interact to induce biochemical liver damage. Food Chem Toxicol 2013;61:144–151.
[47] Rapisarda V, Loreto C, Malaguarnera MM, Ardiri A, Proiti M, Rigano G, et al. Hepatocellular carcinoma and the risk of occupational exposure. World J Hepatol 2016;8:573–590.
[48] VoPham T, Bertrand KA, Hart JE, Laden F, Brooks MM, Yuan J-M, et al. Pesticide exposure and liver cancer: a review. Cancer Causes Control 2017;28:177–190.
[49] Kachuri L, Harris MA, MacLeod JS, Tjepkema M, Peters PA, Demers PA. Cancer risks in a population-based study of 70,570 agricultural workers: results from the Canadian census health and environment cohort (CanCHEC). BMC Cancer 2017;17:343.
[50] Zhao B, Shen H, Liu F, Liu S, Niu J, Guo F, et al. Exposure to organochlorine pesticides is an independent risk factor of hepatocellular carcinoma: a case-control study. J Expo Sci Environ Epidemiol 2012;22:541–548.
[51] Persson EC, Graubard BI, Evans AA, London WT, Weber J-P, LeBlanc A, et al. Dichlorodiphenyltrichloroethane and risk of hepatocellular carcinoma. Int J Cancer 2012;131:2078–2084.
[52] McGlynn KA, Abnet CC, Zhang M, Sun X-D, Fan J-H, O'Brien TR, et al. Serum concentrations of 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) and risk of primary liver cancer. J Natl Cancer Inst 2006;98:1005–1010.
[53] Pukkala E, Martinsen JI, Lynge E, Gunnarsdottir HK, Sparén P, Tryggvadottir L, et al. Occupation and cancer – follow-up of 15 million people in five Nordic countries. Acta Oncol (Madr) 2009;48:646–790.
[54] Lindbohm M-L, Sallmén M, Kyyrönen P, Kauppinen T, Pukkala E. Risk of liver cancer and exposure to organic solvents and gasoline vapors among Finnish workers. Int J Cancer 2009;124:2954–2959.
[55] Lynge E, Rix BA, Villadsen E, Andersen I, Hink M, Olsen E, et al. Cancer in printing workers in Denmark. Occup Environ Med 1995;52:738–744.
[56] Stemhagen A, Slade J, Altman R, Bill J. Occupational risk factors and liver cancer. A retrospective case-control study of primary liver cancer in New Jersey. Am J Epidemiol 1983;117:443–454.
[57] Suarez L, Weiss NS, Martin J. Primary liver cancer death and occupation in Texas. Am J Ind Med 1989;15:167–175.
[58] Døssing M, Petersen KT, Vyberg M, Olsen JH. Liver cancer among employees in Denmark. Am J Ind Med 1997;32:248–254.
[59] Ji J, Hemminki K. Variation in the risk for liver and gallbladder cancers in socioeconomic and occupational groups in Sweden with etiological implications. Int Arch Occup Environ Health 2005;78:641–649.

Please cite this article in press as: European Association for the Study of the Liver. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.08.008

[60] Porru S, Placidi D, Carta A, Gelatti U, Ribero ML, Tagger A, et al. Primary liver cancer and occupation in men: a case-control study in a high-incidence area in Northern Italy. Int J Cancer 2001;94:878–883.
[61] Ferrand J-F, Cénée S, Laurent-Puig P, Loriot M-A, Trinchet JC, Degos F, et al. Hepatocellular carcinoma and occupation in men: a case-control study. J Occup Environ Med 2008;50:212–220.
[62] Kumagai S, Kurumatani N, Arimoto A, Ichihara G. Cholangiocarcinoma among offset colour proof-printing workers exposed to 1,2-dichloropropane and/or dichloromethane. Occup Environ Med 2013;70:508–510.
[63] VoPham T. Environmental risk factors for liver cancer and nonalcoholic fatty liver disease. Curr Epidemiol Reports 2019;6:50–66.
[64] NIOSH pocket guide to chemical hazards. CDC. DHHS (NIOSH) Publication No. 2005-149 2007. Available at: https://www.cdc.gov/niosh/docs/2005-149/pdfs/2005-149.pdf (accessed January 24, 2019).
[65] Zimmerman HJ. Vulnerability of the liver to toxic injury. Hepatotoxic. Advers. Eff. drugs other Chem. liver. 2nd ed., Lippincott Williams and Wilkins; 1999, p. 41–60.
[66] Brautbar N, Williams J. Industrial solvents and liver toxicity: risk assessment, risk factors and mechanisms. Int J Hyg Environ Health 2002;205:479–491.
[67] Hazelhoff MH, Torres AM. Gender differences in mercury-induced hepatotoxicity: potential mechanisms. Chemosphere 2018;202:330–338.
[68] Robles-Diaz M, Lucena MI, Kaplowitz N, Stephens C, Medina-Cáliz I, González-Jimenez A, et al. Use of Hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. Gastroenterology 2014;147:109–118.
[69] Kaufman KR. Carbamazepine, hepatotoxicity, organic solvents, and paints. Seizure 1999;8:250–252.
[70] Mahieu P, Geubel A, Rahier J, Scailteur V, Dieryck JP, Lauwerys R. Potentiation of carbon-tetrachloride hepato-nephrotoxicity by phenobarbital in man, a case report. Int J Clin Pharmacol Res 1983;3:427–430.
[71] Kubo S, Matsuzaki K, Seki T, Ohsawa M, Kumagai S, Endo G. Severe acute hepatitis in a printing company worker: a case study. J Occup Health 2015;57:87–90.
[72] Toskulkao C, Nhongsaeng J, Glinsukon T. Potentiation of carbon tetrachloride induced hepatotoxicity by thinner inhalation. J Toxicol Sci 1990;15:75–86.
[73] Hsieh H-I, Chen P-C, Wong R-H, Wang J-D, Yang P-M, Cheng T-J. Effect of the CYP2E1 genotype on vinyl chloride monomer-induced liver fibrosis among polyvinyl chloride workers. Toxicology 2007;239:34–44.
[74] **Chen M**, **Suzuki A**, Borlak J, Andrade RJ, Lucena MI. Drug-induced liver injury: interactions between drug properties and host factors. J Hepatol 2015;63:503–514.
[75] Schulte P, Howard J. Genetic susceptibility and the setting of occupational health standards. Annu Rev Public Health 2011;32:149–159.
[76] Kogi K, Costa G, Rogers B, Iavicoli S, Kawakami N, Lehtinen S, et al. International code of ethics for occupational health professionals. 3rd ed. (2014). Available at: http://www.icohweb.org/site/code-of-ethics.asp. (Accessed January 22, 2019).
[77] Nielsen MB, Gjerstad J, Frone MR. Alcohol use and psychosocial stressors in the norwegian workforce. Subst Use Misuse 2018;53:574–584.
[78] Bolt HM, Roos PH, Thier R. The cytochrome P-450 isoenzyme CYP2E1 in the biological processing of industrial chemicals: consequences for occupational and environmental medicine. Int Arch Occup Environ Health 2003;76:174–185.
[79] Manno M, Rezzadore M, Grossi M, Sbrana C. Potentiation of occupational carbon tetrachloride toxicity by ethanol abuse. Hum Exp Toxicol 1996;15:294–300.
[80] Hills BW, Venable HL. The interaction of ethyl alcohol and industrial chemicals. Am J Ind Med 1982;3:321–333.
[81] Zimmerman HJ. Effects of alcohol on other hepatotoxins. Alcohol Clin Exp Res 1986;10:3–15.
[82] Tolmanand KG, Dalpiaz AS. Occupational and environmental hepatotoxicity. In: Kaplowitz N, DeLeve LD, editors. Drug-Induced Liver Dis. 3rd ed. Academic; 2013. p. 659–675.
[83] Anders LC, Lang AL, Anwar-Mohamed A, Douglas AN, Bushau AM, Falkner KC, et al. Vinyl chloride metabolites potentiate inflammatory liver injury caused by LPS in mice. Toxicol Sci 2016;151:312–323.
[84] **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.
[85] Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. Gastroenterology 2004;126:1287–1292.
[86] Lammert C, Imler T, Teal E, Chalasani N. Patients with chronic liver disease suggestive of nonalcoholic fatty liver disease may be at higher risk for drug-induced liver injury. Clin Gastroenterol Hepatol 2018.
[87] Vargas JI, Arab JP, Bessone F, Lucena MI, Andrade RJ, Arrese M. Hepatotoxicity in patients with metabolic syndrome: causes and consequences. Curr Hepatol Reports 2017;16:286–292.
[88] Wahlang B, Beier JI, Clair HB, Bellis-Jones HJ, Falkner KC, McClain CJ, et al. Toxicant-associated steatohepatitis. Toxicol Pathol 2013;41:343–360.
[89] Machado MV, Oliveira AG, Cortez-Pinto H. Hepatic steatosis in hepatitis B virus infected patients: meta-analysis of risk factors and comparison with hepatitis C infected patients. J Gastroenterol Hepatol 2011;26:1361–1367.
[90] Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet 2013;381:468–475.
[91] European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO), EASL-EASD-EASO, Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388-1402.
[92] Newsome PN, Cramb R, Davison SM, Dillon JF, Foulerton M, Godfrey EM, et al. Guidelines on the management of abnormal liver blood tests. Gut 2018;67:6–19.
[93] Senior JR. Alanine aminotransferase: a clinical and regulatory tool for detecting liver injury-past, present, and future. Clin Pharmacol Ther 2012;92:332–339.
[94] Robles-Diaz M, Garcia-Cortes M, Medina-Caliz I, Gonzalez-Jimenez A, Gonzalez-Grande R, Navarro JM, et al. The value of serum aspartate aminotransferase and gamma-glutamyl transpetidase as biomarkers in hepatotoxicity. Liver Int 2015;35:2474–2482.
[95] Kleiner DE, Chalasani NP, Lee WM, Fontana RJ, Bonkovsky HL, Watkins PB, et al. Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. Hepatology 2014;59:661–670.
[96] EASL. Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol 2017;66:1047–1081.
[97] Pond SM. Effects on the liver of chemicals encountered in the workplace. West J Med 1982;137:506–514.
[98] Kanz MF, Kaphalia L, Kaphalia BS, Romagnoli E, Ansari GA. Methylene dianiline: acute toxicity and effects on biliary function. Toxicol Appl Pharmacol 1992;117:88–97.
[99] Nomiyama T, Uehara M, Miyauchi H, Imamiya S, Tanaka S, Seki Y. Causal relationship between a case of severe hepatic dysfunction and low exposure concentrations of N, N-dimethylformamide in the synthetics industry. Ind Health 2001;39:33–36.
[100] Andrade RJ, Lucena MI, Kaplowitz N, García-Muṇoz B, Borraz Y, Pachkoria K, et al. Outcome of acute idiosyncratic drug-induced liver injury: long-term follow-up in a hepatotoxicity registry. Hepatology 2006;44:1581–1588.
[101] Andrade RJ, Lucena MI, Martin-Vivaldi R, Fernandez MC, Nogueras F, Pelaez G, et al. Acute liver injury associated with the use of ebrotidine, a new H2-receptor antagonist. J Hepatol 1999;31:641–646.
[102] Szymańska JA. Hepatotoxicity of brominated benzenes: relationship between chemical structure and hepatotoxic effects in acute intoxication of mice. Arch Toxicol 1998;72:97–103.
[103] Kamijima M, Hisanaga N, Wang H, Nakajima T. Occupational trichloroethylene exposure as a cause of idiosyncratic generalized skin disorders and accompanying hepatitis similar to drug hypersensitivities. Int Arch Occup Environ Health 2007;80:357–370.
[104] Pimentel JC, Menezes AP. Liver disease in vineyard sprayers. Gastroenterology 1977;72:275–283.
[105] Zimmerman HJ. Syndromes of enviromental hepatotoxicity. Hepatotoxic. Advers. Eff. drugs other Chem. liver. 2nd ed., Lippincott Williams and Wilkins; 1999, p. 327–364.
[106] Mullick FG, Ishak KG, Mahabir R, Stromeyer FW. Hepatic injury associated with paraquat toxicity in humans. Liver 1981;1:209–221.
[107] Redlich CA, West AB, Fleming L, True LD, Cullen MR, Riely CA. Clinical and pathological characteristics of hepatotoxicity associated with occupational exposure to dimethylformamide. Gastroenterology 1990;99:748–757.

Please cite this article in press as: European Association for the Study of the Liver. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.08.008

[108] Lundqvist G, Flodin U, Axelson O. A case-control study of fatty liver disease and organic solvent exposure. Am J Ind Med 1999;35:132–136.
[109] Malaguarnera G, Cataudella E, Giordano M, Nunnari G, Chisari G, Malaguarnera M. Toxic hepatitis in occupational exposure to solvents. World J Gastroenterol 2012;18:2756–2766.
[110] Cave M, Falkner KC, Ray M, Joshi-Barve S, Brock G, Khan R, et al. Toxicant-associated steatohepatitis in vinyl chloride workers. Hepatology 2010;51:474–481.
[111] Younes R, Bugianesi E. NASH in lean Individuals. Semin Liver Dis 2019;39:86–95.
[112] Carvalho FM, Silvany Neto AM, Mendes JLB, Cotrim HP, Nascimento ALC, Lima Júnior AS, et al. Liver enzyme abnormalities among oil refinery workers. Rev Saude Publica 2006;40:92–98.
[113] Cotrim HP, Carvalho F, Siqueira AC, Lordelo M, Rocha R, De Freitas LAR. Nonalcoholic fatty liver and insulin resistance among petrochemical workers. JAMA 2005;294:1618–1620.
[114] 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.
[115] Cotrim HP, De Freitas LAR, Freitas C, Braga L, Sousa R, Carvalho F, et al. Clinical and histopathological features of NASH in workers exposed to chemicals with or without associated metabolic conditions. Liver Int 2004;24:131–135.
[116] Mastrangelo G, Fedeli U, Fadda E, Valentini F, Agnesi R, Magarotto G, et al. Increased risk of hepatocellular carcinoma and liver cirrhosis in vinyl chloride workers: synergistic effect of occupational exposure with alcohol intake. Environ Health Perspect 2004;112:1188–1192.
[117] Fedeli U, Girardi P, Gardiman G, Zara D, Scoizzato L, Ballarin MN, et al. Mortality from liver angiosarcoma, hepatocellular carcinoma, and cirrhosis among vinyl chloride workers. Am J Ind Med 2019;62:14–20.
[118] Straif K, Chambless L, Weiland SK, Wienke A, Bungers M, Taeger D, et al. Occupational risk factors for mortality from stomach and lung cancer among rubber workers: an analysis using internal controls and refined exposure assessment. Int J Epidemiol 1999;28:1037–1043.
[119] Tandon RK, Tandon BN, Tandon HD, Bhatia ML, Bhargava S, Lal P, et al. Study of an epidemic of venoocclusive disease in India. Gut 1976;17:849–855.
[120] **Zhuge YZ**, **Wang Y**, Zhang F, Zhu CK, Zhang W, Zhang M, et al. Clinical characteristics and treatment of pyrrolizidine alkaloid-related hepatic vein occlusive disease. Liver Int 2018;38:1867–1874.
[121] Paliard P, Valette PJ, Berger F, Contassot JC, Partensky C. Peliosis hepatis of late onset in a patient exposed to vinyl chloride and treated for hepatic angiosarcoma. Gastroenterol Clin Biol 1991;15:445–448.
[122] De Gottardi A, Rautou PE, Schouten J, Rubbia-Brandt L, Leebeek F, Trebicka J, et al. Porto-sinusoidal vascular disease: proposal and description of a novel entity. Lancet Gastroenterol Hepatol 2019;4:399–411.
[123] Blendis LM, Smith PM, Lawrie BW, Stephens MR, Evans WD. Portal hypertension in vinyl chloride monomer workers. A hemodynamic study. Gastroenterology 1978;75:206–211.
[124] Popper H, Thomas LB. Alterations of liver and spleen among workers exposed to vinyl chloride. Ann N Y Acad Sci 1975;246:172–194.
[125] Manner J, Radlwimmer B, Hohenberger P, Mössinger K, Küffer S, Sauer C, et al. MYC high level gene amplification is a distinctive feature of angiosarcomas after irradiation or chronic lymphedema. Am J Pathol 2010;176:34–39.
[126] Käcker C, Marx A, Mössinger K, Svehla F, Schneider U, Hogendoorn PCW, et al. High frequency of MYC gene amplification is a common feature of radiation-induced sarcomas. Further results from EORTC STBSG TL 01/01. Genes Chromosomes Cancer 2013;52:93–98.
[127] Gelin M, Van de Stadt J, Rickaert F, De Prez C, Levarlet M, Adler M, et al. Epithelioid hemangioendothelioma of the liver following contact with vinyl chloride. Recurrence after orthotopic liver transplantation. J Hepatol 1989;8:99–106.
[128] Guido M, Sarcognato S, Pelletti G, Fassan M, Murer B, Snenghi R. Sequential development of hepatocellular carcinoma and liver angiosarcoma in a vinyl chloride-exposed worker. Hum Pathol 2016;57:193–196.
[129] Evans DM, Williams WJ, Kung IT. Angiosarcoma and hepatocellular carcinoma in vinyl chloride workers. Histopathology 1983;7:377–388.
[130] Ito D, Tanaka T, Akamatsu N, Ito K, Hasegawa K, Sakamoto Y, et al. Recurrent acute liver failure because of acute hepatitis induced by organic solvents: a case report. Medicine (Baltimore) 2016;95:e2445.
[131] Døssing M. Occupational toxic liver damage. J Hepatol 1986;3:131–135.
[132] McGill MR, Woolbright BL, Weemhoff JL, Jaeschke H. Mechanistic biomarkers in liver diseases. Dordrecht: Springer; 2017. p. 71–97.
[133] Health and safety at work-scientific committee on occupational exposure limits. Available at: https://ec.europa.eu/social/main.jsp?catId=148&intPageId=684&langId=en (accessed January 22, 2019).
[134] **Delahaye L**, **Janssens B**, Stove C. Alternative sampling strategies for the assessment of biomarkers of exposure. Curr Opin Toxicol 2017;4:43–51.
[135] Sabbioni G, Turesky RJ. Biomonitoring human albumin adducts: the past, the present, and the future. Chem Res Toxicol 2017;30:332–366.
[136] Boogaard PJ. Use of haemoglobin adducts in exposure monitoring and risk assessment. J Chromatogr B Analyt Technol Biomed Life Sci 2002;778:309–322.
[137] Thier R, Lewalter J, Selinski S, Bolt HM. Re-evaluation of the effect of smoking on the methylation of N-terminal valine in haemoglobin. Arch Toxicol 2001;75:270–273.
[138] De Smedt T, De Cremer K, Vleminckx C, Fierens S, Mertens B, Van Overmeire I, et al. Acrylonitrile exposure in the general population following a major train accident in Belgium: a human biomonitoring study. Toxicol Lett 2014;231:344–351.
[139] Sabbioni G, Dongari N, Sepai O, Kumar A. Determination of albumin adducts of 4,4′-methylenediphenyl diisocyanate in workers of a 4,4′-methylenedianiline factory. Biomarkers 2016;21:731–738.
[140] Ma J, Xia Q, Fu PP, Lin G. Pyrrole-protein adducts – A biomarker of pyrrolizidine alkaloid-induced hepatotoxicity. J Food Drug Anal 2018;26:965–972.
[141] EASL-ALEH. Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63:237–264.
[142] European Association for the Study of the Liver. EASL Clinical practice guidelines: liver transplantation. J Hepatol 2016;64:433–485.
[143] American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs). Available at: https://www.chemsafetypro.com/Topics/USA/ACGIH_TLVs_Threshold_Limit_Values.html (accessed January 24, 2019).
[144] Lauwerys RR, Hoet P. Industrial chemical exposure: guidelines for biological monitoring. 3rd ed. Lewis Publishers; 2001.
[145] Boogaard PJ, Money CD. A proposed framework for the interpretation of biomonitoring data. Environ Heal 2008;7:S12.

Please cite this article in press as: European Association for the Study of the Liver. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.08.008