EASL CPG on Occupational Liver Diseases

Massimo Colombo, MD

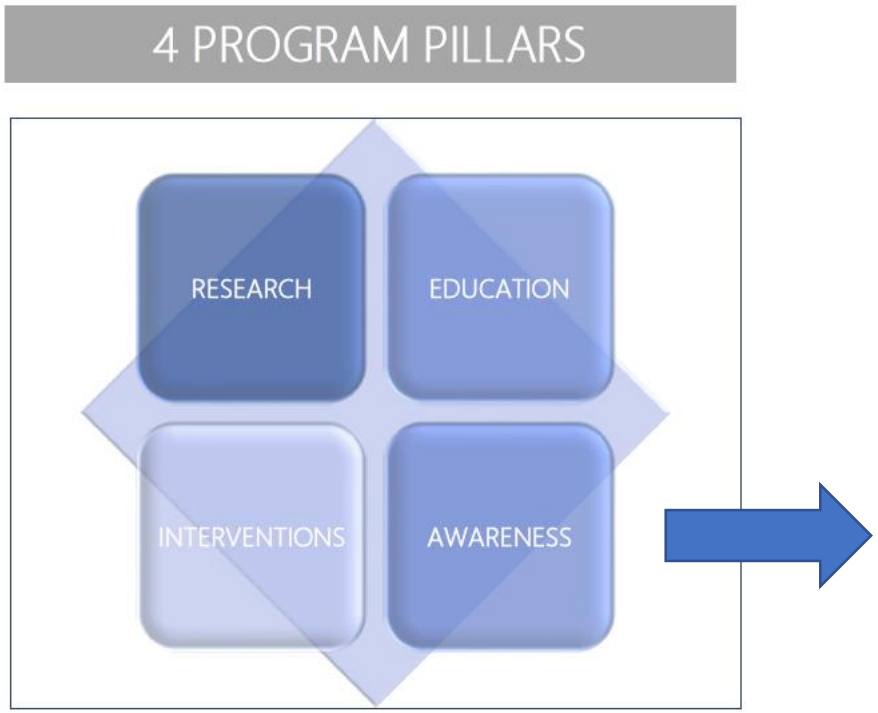
Head,Center for Translational Research in Hepatology Humanitas Rozzano, Italy.

Chairman,EASL International Liver Foundation, Geneva, Switzerland

Financial Disclosures

Advisory committees:	Merck, Roche, Novartis, Bayer, BMS, Gilead Science, Tibotec, Vertex, Janssen, Achillion, Lundbeck, GSK, GenSpera, AbbVie, Alfa Wasserman,Intercept, Target HCC,COST
Speaking and teaching:	Tibotec, Roche, Novartis, Bayer, BMS, Gilead Science, Vertex, Merck, Janssen, AbbVie,Intercept

EASL Foundation Committed to Shed New Light on OLD



Shedding new light on occupational liver disease

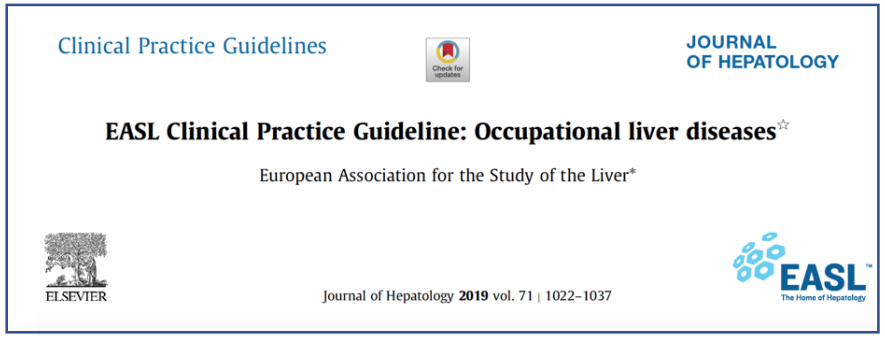
By leveraging skills and capabilities in the EASL scientific community, we are raising awareness of the importance of applying an evidence-based approach in the assessment of hepatic risks associated with occupational and environmental exposures.

Why a Clinical Practice Guideline on Occupational Liver Diseases (OLD) ?

- Hepatotoxicity is the most common organ injury due to occupational and environmental exposures to industrial chemicals. Recommendations from liver societies not available.
- Like DILI and ethanol,OLD recapitulates an injury linked to gene/enviroment interaction.
- As of May 2011 > 60 million unique chemicals were registered with the Chemical Abstracts Service Registry.
- 33% of the 677 most common workplace chemicals reported in the National Institute of Occupational Safety and Health Pocket Guide are associated with hepatotoxicity. (Tolman and Sirrine 1998)
- ***The prevalence of OLD is undefined*.**

1. Centre for evidence Based Medicine. Levels of evidence n.d. https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/,2.Aithal, et al. Clin Pharmacol Ther 2011;89:806–15.

EASL Clinical Practice Guideline on Occupational Liver Diseases (OLD)



Chair : Massimo Colombo , Milan

Panel members : Carlo La Vecchia , Milan
Marcello Lotti , Padua
M Isabel Lucena , Malaga
Christophe Stove , Ghent
Valerie Paradis , Clichy
Phil Newsome , Birmingham

Oxford grading of evidence

The Mission of CPG on OLD

SCOPE

- Occupational chemical-induced liver injuries

  Not covered: viral infections in HCW and environmental pollutants

AIMS

- To provide **standardization of nomenclature, definitions and classification** of the type of liver injuries, based in part on the criteria used for DILI
- To **increase awareness of OLD** within the medical community and **to improve recognition and management** of affected patients in a standardized manner

1. Centre for evidence Based Medicine. Levels of evidence n.d. https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/,2.Aithal, et al. Clin Pharmacol Ther 2011;89:806–15.

Occupational Liver Diseases

Outline

1. Challenges in obtaining the occupational history and diagnosis
2. Clinical pathological spectrum
3. Liver tumours associated with exposure

Collecting the Occupational History - 1

STRUCTURE OF THE OCCUPATIONAL HISTORY

- A chronological summary of all work activities and their duration
- A detailed description of the work place, of the job and of a typical working day
- An inventory of all chemicals that are present and how are used.
- Details of any measures to limit chemical exposure such as: work place ventilation and the nature protective measures that are taken
- Enquiring if programs of industrial hygiene, biological monitoring and medical surveillance are or have been in place and retrive the result

EASL CPG on OLD J Hepatol 2019

Collecting the Occupational History - 2

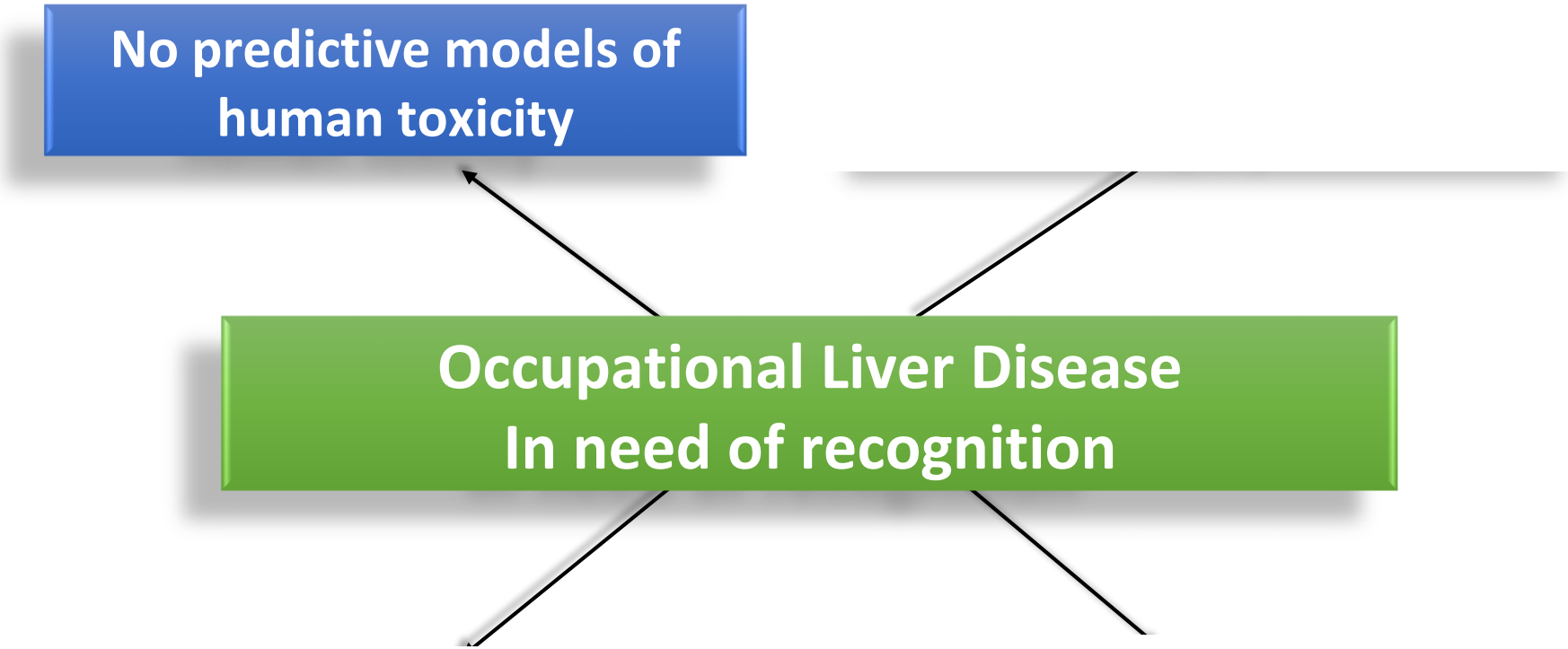
- Enquire as to whether coworkers have similar symptoms and signs to those of a patient with suspected OLD.
- Enquire if compensation procedures have been undertaken and results are available.
- Exposures to chemicals other than those present at work places, associated for instance with environmental air pollution, hobbies, recreational habits and others should be ruled out.

Recommendation		
• Assessment of OLD is improved by input from a **multidisciplinary team** including hepatologists, pathologists, occupational medicine physicians, toxicologists and epidemiologists	Level 5 (expert opinion)	D

EASL CPG on OLD J Hepatol 2019

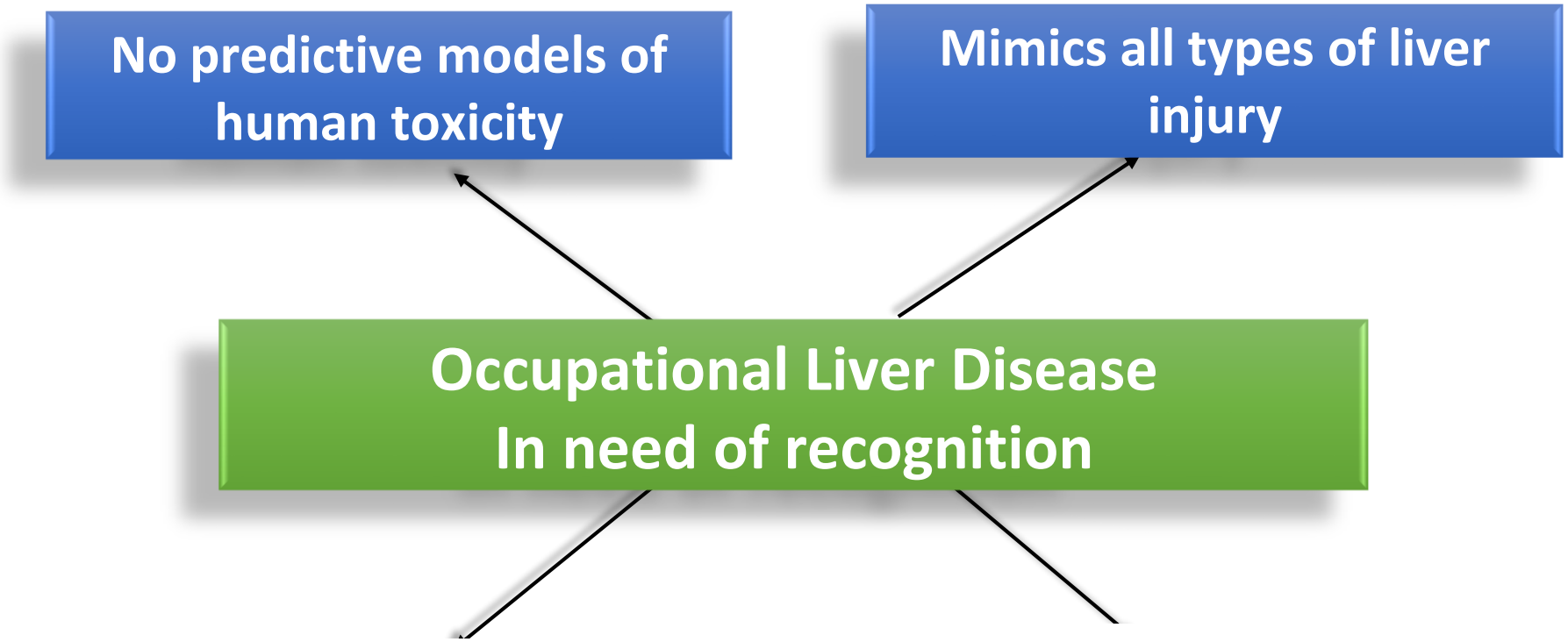
Why Diagnosis of OLD Remains Challenging

Why Diagnosis of OLD Remains Challenging



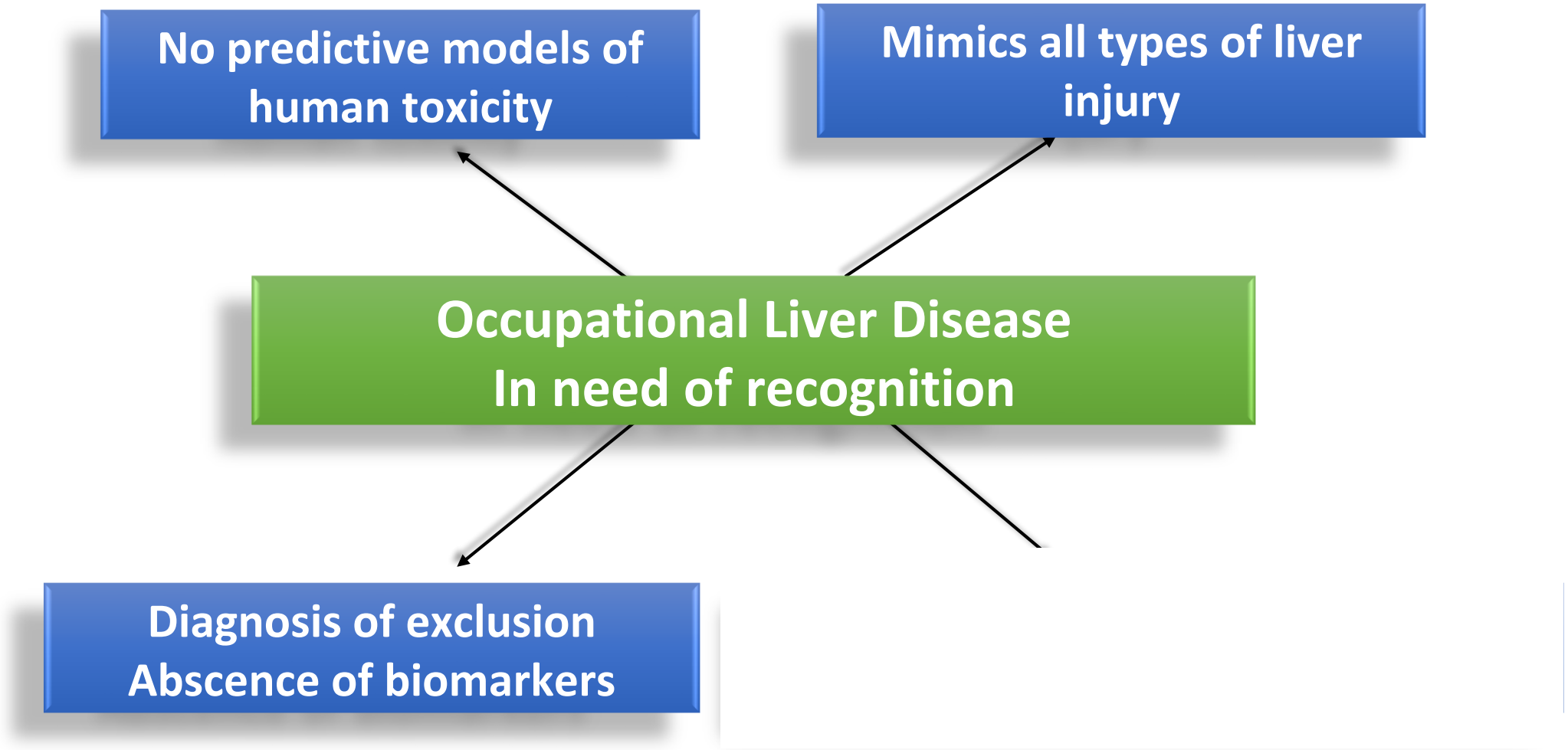
EASL CPG OLD ILC J Hepatol 2019

Why Diagnosis of OLD Remains Challenging



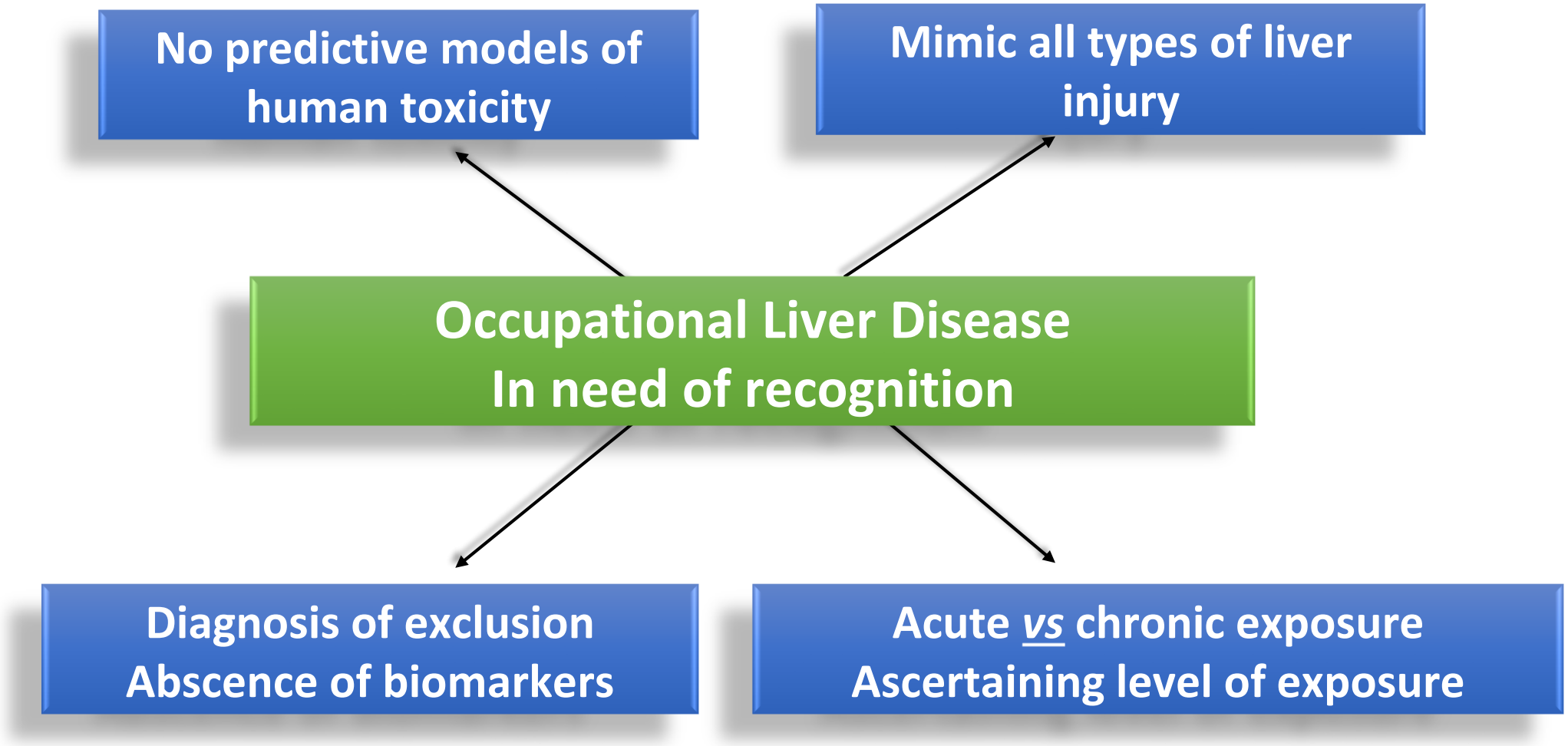
EASL CPG OLD ILC J Hepatol 2019

Why Diagnosis of OLD Remains Challenging



EASL CPG OLD J Hepatoll 2019

Why Diagnosis of OLD Remains Challenging



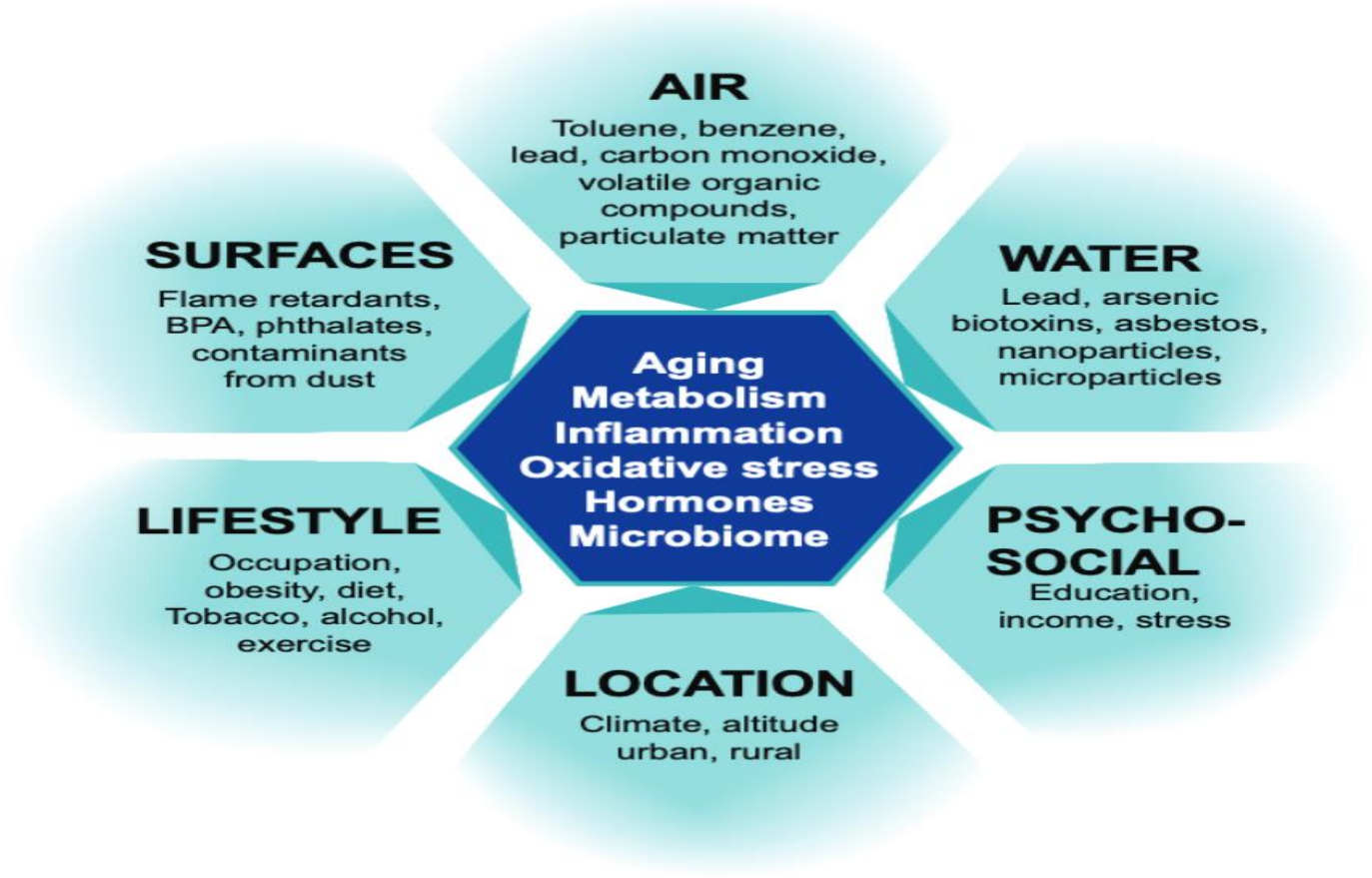
EASL CPG OLD ILC J Hepatol 2019

Occupational Liver Diseases

Outline

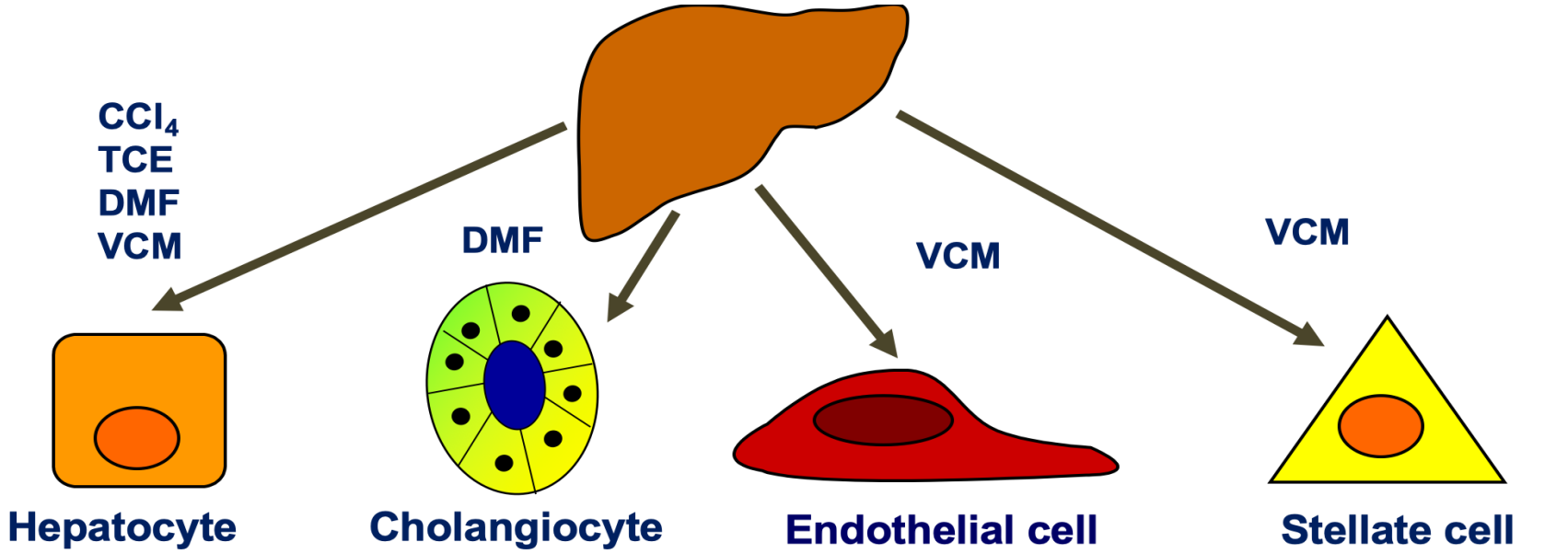
1. Challenges in obtaining the occupational history and diagnosis
2. Clinical pathological spectrum
3. Liver tumours associated with exposure

How Workers Get Exposed to Toxicants and Risk Modifiers



Cheung AC et al Hepatology 2019

Clinico-Pathological Spectrum of OLD



Hepatocyte	Cholangiocyte	Endothelial cell	Stellate cell
Hepatitis Cholestasis Steatosis TASH Neoplasia	Sclerosing cholangitis	Sinusoidal obstruction s. Peliosis Epithelioid hemangioendothelioma Angiosarcoma	Periportal fibrosis Cirrhosis

Courtesy of Prof M Lucena

EASL CPG on OLD J Hepatol 2019

Acute OLD Rarely Occurs

Pathological pattern	Morphological feature	Toxicant
Hepatocellular	Hepatocellular necrosis ± lobular inflammation	CCl_4, chloroform, toluene, TNT, PCBs, chloronaphtalene, DMF, hydrazine, 2-nitropropane, phosphorus, DMA, halothane, TCE, tetrachloroethane, 1,4-dichlorobenzene
	Microvesicular steatosis	DMF
Cholestatic/ Mixed	Cholestasis, cholangitis	Methylenedianiline
	Combined features	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, lead (to be confirmed?), POPs, pesticides, and some nitro-organic compounds
Vascular	Sinusoidal obstruction syndrome	VCM, dioxin, pyrrolizidine alkaloids, arsenic, copper sulfate
	Peliosis	VCM

Chronic Non Malignant OLD

- Possible **excess risk of cirrhosis** in workers exposed to VCM,bar staff of both sexes,male seafarers, caterers ,cooks and kitchen porters (likely alcohol related).
- No consistent associations with other exposures

Toxicant associated steatohepatitis (TASH)

- Hepatic steatosis following different industrial chemical exposures[1] Observations in Brazilian petrochemical workers[2]
- Asymptomatic or insidious onset, with normal liver tests that makes under-recognition probable

EASL CPG on OLD J Hepatol 2019

Selected Chemicals Associated with TASH in Humans or Animal Models

Steatohepatitis with normal transaminases	Steatohepatitis with elevated (or unknown) transaminases
Vinyl chloride	Carbon tetrachloride
Tetrachloroethylene	Dimethylformamide
Solvents (occasionally including VOCs)	Methylmercury
Nitrobenzene	Pesticides: chlordecone, atrazine, paraquat
Nitromethane	Polychlorinated biphenyls
	Yellow phosphorus
	1,1,2-Trichloroethane
	VOCs (occasionally)
	Arsenic
	Lead

Adapted from Cave, M., K. C. Falkner, and C. J. McClain, Occupational and Environmental Liver Disease. In *Zakim and Boyer's Hepatology: A Textbook of Liver Disease*. 6th edn. Philadelphia. Elsevier Saunders; 2011

Toxicant Associated Steatohepatitis (TASH) in Petrochemicals Workers +/- Associated Metabolic Conditions

Risk factors associated with NASH : G1 Exposure to chemicals

G2 Exposure + metabolic conditions

G3 No exposure, + metabolic conditions

	G1 n=31	G2 n=30	G3 n=23
Age (y)	37	39	48 P 0.002
Male	30 (97)	30 (100)	17 (74)
Obesity	0	8 (27%)	10 (43)
Hyperlipidemia	0	20 (67%)	7 (30)
Diabetes	0	2 (6 %)	6 (26)

Histological findings (n,%)	G1 n=31	G2 n=30	G3 n=23
Steatohepatitis	9 (29)	6 (20)	11 (48)
Steatohepatitis + fibrosis	22 (71)	24 (80)	12 (52)
Cirrhosis	0	0	2
Cholestasis	16 (52)	12 (40)	3 (13) P=0.002

Cotrim HP et al Liver Intern 2004, 24, 131–135; Cotrim HP et al. JAMA 2005

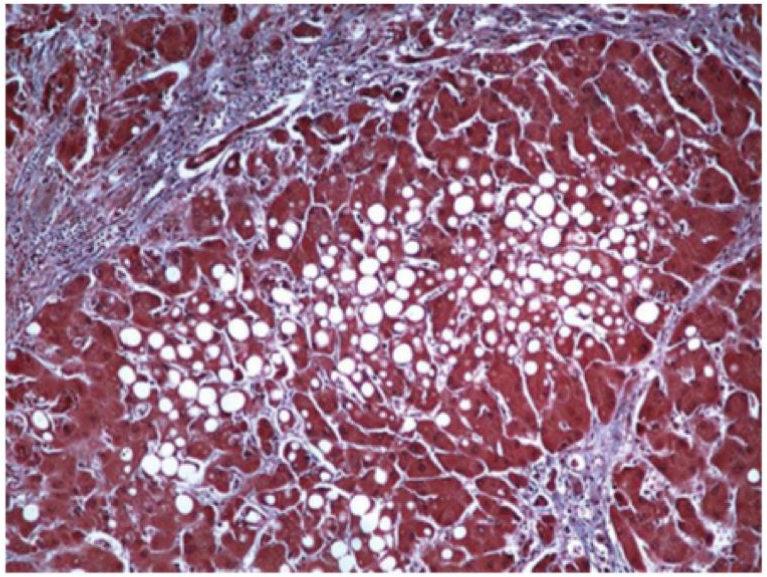
Toxicant Associated Steatohepatitis (TASH) in Non Obese VC Workers

Highly exposed : steatohepatitis in 80%. Of these, 55% had fibrosis and 18% had hemangiosarcoma.

Table 6. Serum Proinflammatory Cytokine and Antioxidant Activity Levels

Laboratory Variable	Healthy Unexposed Controls	Healthy Chemical Worker Controls	TASH
TNF-α (pg/mL)	4.1 (1.5)	3.0 (1.2)	11.2 (18.0)*
IL-1β (pg/mL)	0.1 (0.1)	0.4 (0.6)	9.1 (11.9)†,‡
IL-6 (pg/mL)	1.4 (1.6)	3.5 (3.0)	10.9 (10.6)†,§
IL-8 (pg/mL)	2.7 (1.9)	3.7 (1.6)	12.0 (12.9)†,§
MCP-1 (pg/mL)	276.5 (121.5)	329.4 (137.9)	302.3 (148.0)
Antioxidant activity (mM)	4.1 (0.3)	3.5 (0.8)	2.6 (0.3)‡,‖

Liver Biopsy of a Vinyl Chloride Worker with TASH and Cirrhosis



100x hematoxylin-eosin

Cave M et al Hepatology 2010

Occupational Liver Diseases

Outline

1. Challenges in obtaining the occupational history and diagnosis
2. Clinical pathological spectrum
3. Liver tumours associated with exposure

Hepatic Angiosarcoma(HAS)

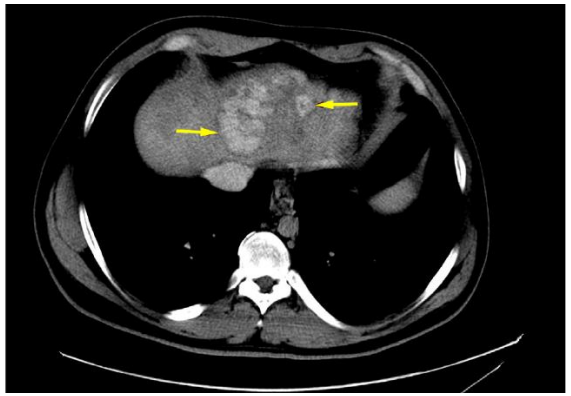
M : F = 4 to 1 , 60–70 yr

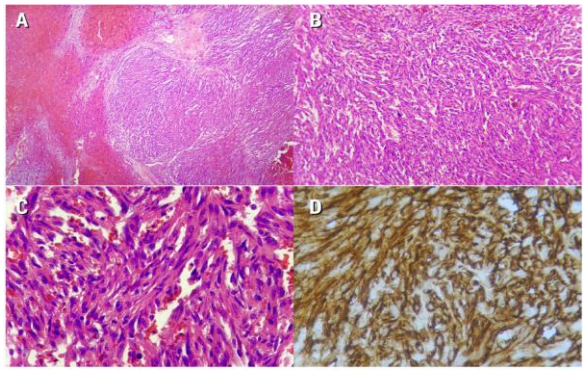
- Background liver disease
- Abdominal pain,weight loss,malaise,portal hypertension, hemoperitoneum, extrahepatic metas.

Diff.diagnosis HEHE,KS,benign vascular tumors,metas.

Risk factors Thorotrast,VC monomers,arsenic,radiations, drugs and chronic liver diseases.

Hypervascular mass in S2 and S3





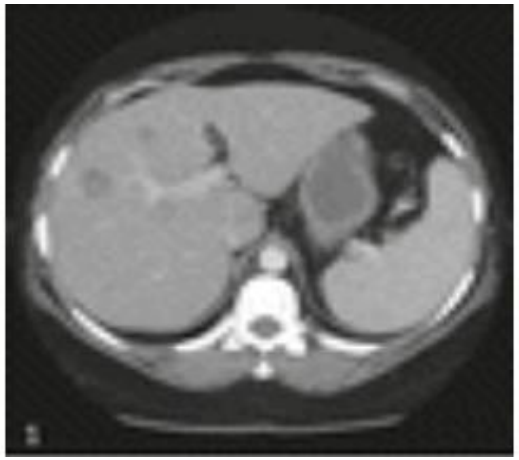
X100 HE stain. Fusiform cells with pleiomorphic nuclei lining the sinusoids,areas of hemorrhage and necrosis.

Lazar DC et al WJCO 2019

Hepatic Epitelioid Hemangioendotelioma(HEHE)

M : F = 3 to 2 , 30–40 yr

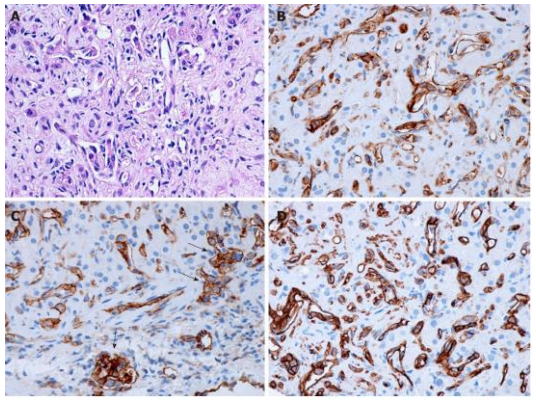
- No background liver disease
- From no symptoms to oligosymptomatic ⟹ portal hypertension,VOD



Lollipop sign

Diff. diagnosis AS, KS, metas,VOD,Budd Chiari

Risk factors OC,alcohol,VH, VC & asbestos



Lazar DC et al WJCO 2019

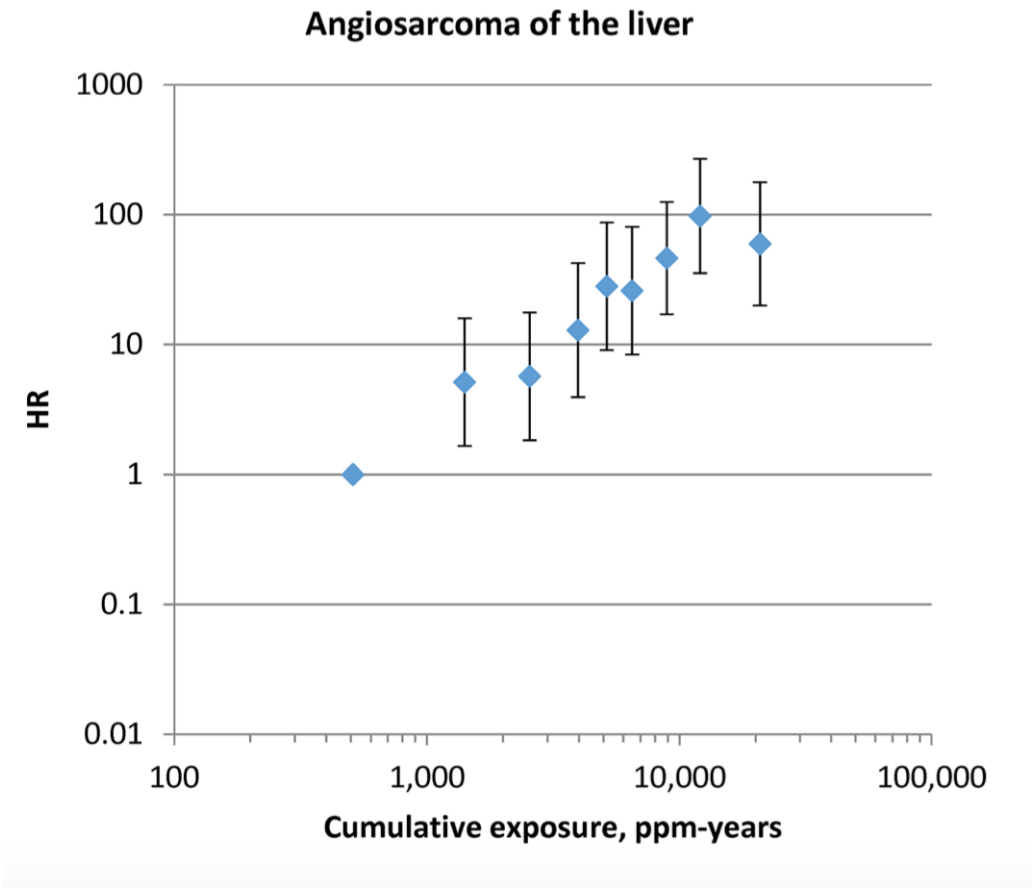
Liver Cancer Mortality in Vinyl Chloride Exposed Workers 35 Plants in the USA

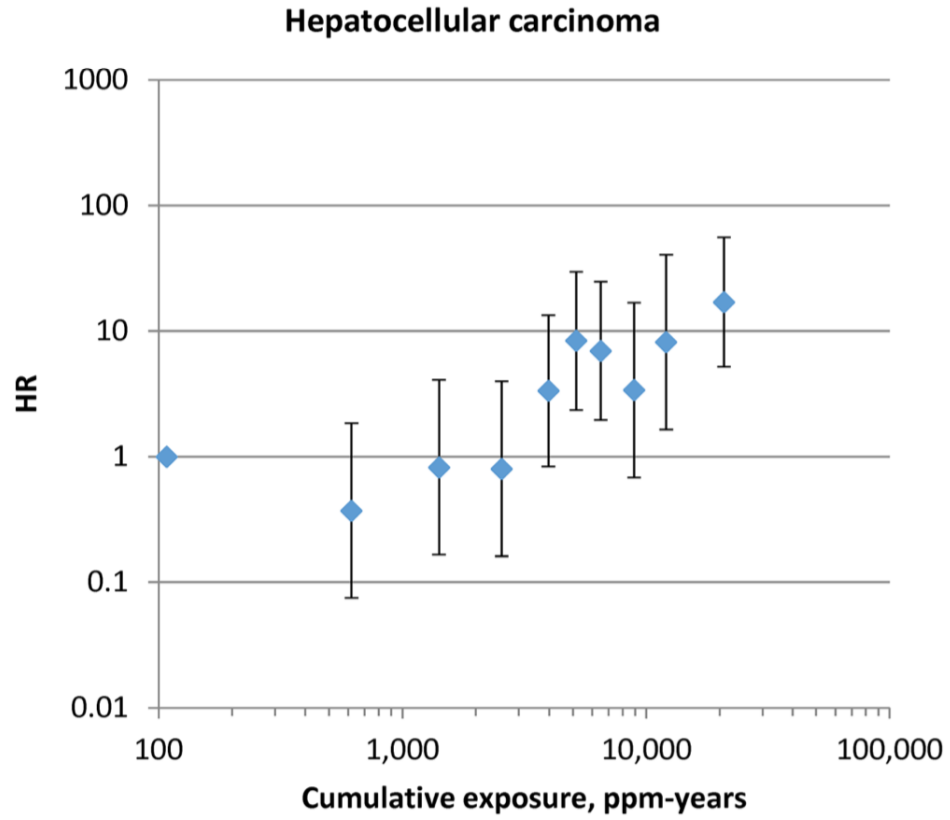
- 9951
- The a
- The a
- 5636 …r 99.4%.
- 1196

Cause of death	Observed	Expected	SMR	95% CI
All causes	5636	6493.2	**0.87**	**0.85 to 0.89**
All malignant neoplasms	1713	1741.0	**0.98**	0.94 to 1.03
Oral cavity and pharynx	35	35.3	**0.99**	0.69 to 1.38
Oesophagus	55	48.6	**1.13**	0.85 to 1.47
Stomach	34	45.2	**0.75**	0.52 to 1.05
Intestine except rectum	115	140.2	**0.82**	**0.68 to 0.98**
Rectum	30	30.1	**1.00**	0.67 to 1.42
Liver, biliary passages and gall bladder	135	47.0	**2.87**	**2.40 to 3.40**
Liver only‡	117	31.8	**3.68**	**3.04 to 4.41**

Mundt KA, et al. Occup Environ Med 2017;**74**:709–716.

Liver Cancer Mortality in Vinyl Chloride Exposed Workers 35 Plants in the USA



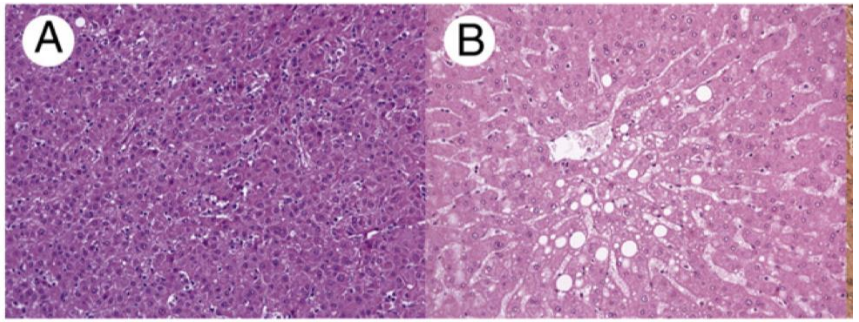


Mundt KA, et al. Occup Environ Med 2017;**74**:709–716.

Sequential Development of HCC and Liver Angiosarcoma in a Vinyl Chloride Exposed Worker

- 78 y.o. autoclave cleaner exposed from 1991 to 1996 to vinyl chloride (4100 ppm/yr)
- However : *KRAS* G12D point mutation in AS not in HCC

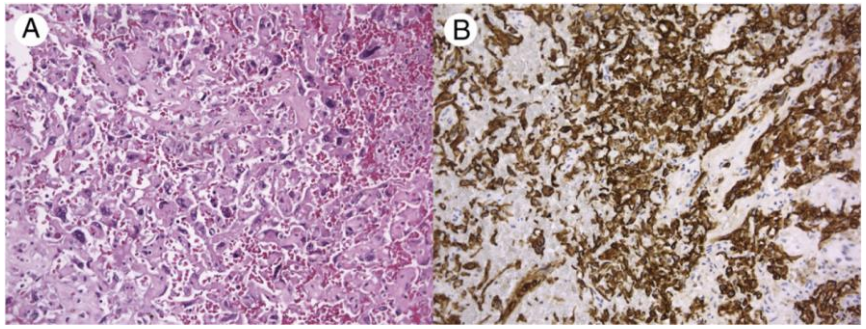
2009



HCC 4 cm S7

TASH
Micronuclei

2012



Angiosarcoma

Guido M et al Human Pathol 2006

OLD.Liver Malignancies

Vinyl chloride monomer(VCM) and liver AS and HCC

- High exposure to VCM until the early 70's has been associated to a substantial excess risk of liver AS [63/10,000 US workers, f-up 40 yrs][1].
- Possible association with HCC.

Controversial associations with liver cancers

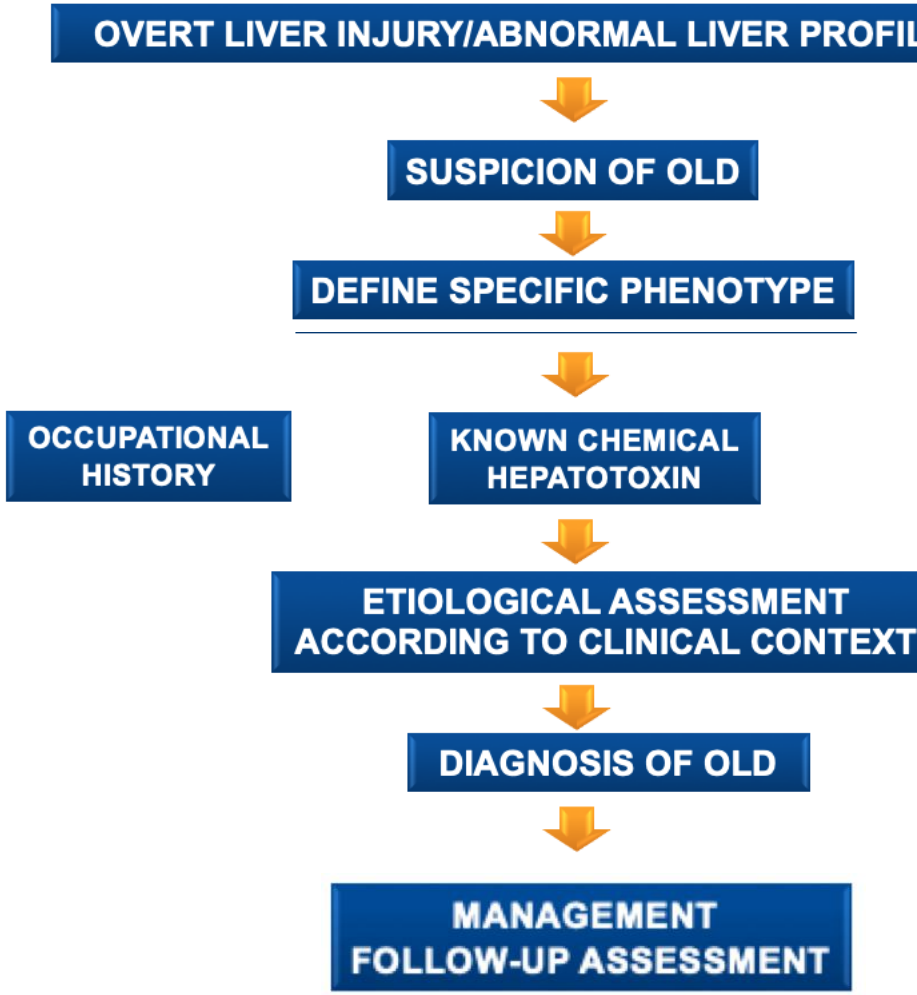
- Trichloroethylene and other chlorinated solvent-exposed workers, workers exposed to polychlorinated biphenyl and workers exposed to pesticides.

EASL CPG OLD J Hepatol 2019 ; 1. Mundt KA et al. Occup Environ Med 2017

Surveillance with US for Workers Highly Exposed to VCM

Recommendation	Grade of evidence	Grade of recommendation
Surveillance with ultrasounds for development of emergent liver neoplasms is recommended 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).	Level 2 (Historic cohort studies)	C

Approach to the Assessment and Diagnosis of OLD



- Acute liver injury
- TASH
- Fibrosis/cirrhosis
- Vascular disease
- Neoplasm

Rule out:
- Viral/infectious hepatitis
- Biliary obstruction
- Alcoholic hepatitis
- Autoimmune hepatitis
- Ischaemic injury
- DILI

Liver biopsy:

Usually required to characterize the phenotype

Confounding factors:
- NAFLD
- Alcohol abuse
- Pre-existing chronic liver disease
- Drug therapy: tamoxifen, amiodarone, methotrexate

Search for:

- Presence of other organ involvement
-Hypersensitivity / autoimmune manifestations

EASL CPG on OLD J Hepatol 2019

Take Home Message

- Collecting the occupational history is crucial. Patients must be assessed by a multidisciplinary team.
- Acute liver disease is rare compared to chronic liver injury. There are many sensitizing cofactors.
- Liver angiosarcoma is clearly associated with high exposure to vinyl chloride (in the past only), HCC is possible, cirrhosis is unlikely.
- Hepatitis and cholestasis are the dominant occupational lesions, often obscured by comorbidities such as alcohol and metabolic steatohepatitis.
- The unmet needs : availability of specific tests of toxicity.

Unmet Needs and Future Research

- A step forward in improving safety in the workplace is collecting cohort data from **occupational exposure registries** including clinical, biochemical and follow-up information in order to obtain incidence figures of hepatotoxicity and trends in re (emerging) OLD.

- The **development and quantification of sensitive and specific biomarkers of liver damage** caused by toxicants that may help in fine-tuning of differential diagnosis, without the need for histological examination of the liver.Could provide clues to prognosis.

- Advancements in the field of biomarkers would allow more effective **risk stratification** algorithms, while providing **mechanistic insights** that would help the development of safe and effective treatments.

EASL CPG on OLD J Hepatol 2019