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The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals

155. Occupational chemical exposures in combination with unusual working hours

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Preface

The main task of the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) is to produce criteria documents to be used by the regulatory authorities as the scientific basis for setting occupational exposure limits for chemical agents. For each document, NEG appoints one or several authors. An evaluation is made of all relevant published, peer-reviewed original literature found. Whereas NEG adopts the document by consensus procedures, thereby granting the quality and conclusions, the authors are responsible for the factual content of the document. The views presented reflect the opinions of NEG and authors, but not necessarily those of the Nordic authorities or institutes.

The evaluation of the literature and the drafting of this document on *Occupational chemical exposures in combination with unusual working hours* were done by Dr Jenny-Anne S. Lie, Dr Shan Zienolddiny-Narui at the National Institute of Occupational Health, Norway and Dr Magne Bråtveit at the University of Bergen, Norway.

The draft versions were discussed within NEG and the final version was adopted on 25 September 2023. Editorial work and technical editing were performed by the NEG secretariat. The following experts participated in the elaboration of the document:

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All criteria documents produced by the Nordic Expert Group may be downloaded from *www.nordicexpertgroup.org*.

Gunnar Johanson, Chairman of NEG

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Abbreviations and acronyms

ACGIH	American Conference of Governmental Industrial Hygienists
AEGL	acute exposure guideline levels
AIOH	Australian Institute of Occupational Hygienists
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLV	biological limit value
Bmal	brain and muscle Arnt-like
CI	confidence interval
CJL	chronic jet-lag
COHb	carboxyhaemoglobin
Cry	cryptochrome
CYP	cytochrome P450
DCM	dichloromethane (methylene chloride)
DEN	diethylnitrosamine
DNEL	derived no-effect level
ECG	electrocardiogram
ECHA	European Chemicals Agency
EU	European Union or endotoxin unit
EU-LFS	European Union Labour Force Survey
$FEF_{25–75}$	forced expiratory flow between 25% and 75% of VC
FEV_1	forced expiratory volume in 1 second (1^{st} sec after full expiration)
GSH	glutathione
HDL	high density lipoprotein
HI	hazard index
IRSST	Institut de recherche Robert-Sauvé en santé et en sécurité du travail
LC_{50}	lethal concentration for 50% of the animals at single inhalation exposure
LD12:12	12:12 hours light-dark cycle
LDL	low density lipoprotein
LORR	loss of righting reflex
MAK	Maximale Arbeitsplatz-Konzentration (maximum workplace concentration)
metHb	methaemoglobin
MT	metallothionein
NAC/AEGL	National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances
NRC	National Research Council
OEL	occupational exposure limit
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PBPK	physiologically based pharmacokinetic
PBTK	physiologically based toxicokinetic

PEF	peak expiratory flow
Per	period
PEV	permissible exposure value
POR	cytochrome P450 oxidoreductase
PPAR	peroxisome proliferator-activated receptor
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SCOEL	Scientific Committee on Occupational Exposure Limits
SDH	sorbitol dehydrogenase
STEL	short-term exposure limit (normally the 15-min TWA)
TLV	threshold limit value
TWA	time-weighted average
U-TTCA	urinary 2-thiothiazolidine-4-carboxylic acid
VC	vital capacity
WT	wild type
ZT	zeitgeber time (ZT0: light on and ZT12: light off)

Terms used in this document

Chronotoxicity
The toxic effects of chemicals on living organisms in relation to time of day.

Circadian clock
The circadian clock has an internally driven 24-hour circadian rhythm that tends to run longer than 24 hours but resets every day by the sun's light/dark cycle. The internal body clock sets the timing for many circadian rhythms, which regulate processes such as sleep/wake cycles, hormonal activity and body temperature rhythm.

Circadian rhythms
Circadian rhythms are internally driven cycles in various organs that rise and fall during a 24-hour day. The master circadian clock in the brain synchronises and controls these cycles so they work together.

Clock gene
Any of a number of genes that interact with each other to make up an auto-regulatory feedback loop, in which its activation and repression cycle takes about 24 hours. Examples of clock genes are *clock (clock), brain and muscle Arnt-like protein 1 (Bmal1), period 1* and *2 (Per1* and *Per2)* and *cryptochrome 1* and *2 (Cry1* and *Cry2)*.

Zeitgeber
An environmental agent or event (such as the occurrence of light or dark) that provides the stimulus that sets or resets a biological clock of an organism.

1. Introduction

Occupational exposure limits (OELs) usually assume an 8-hour workday, 5 days/week and a 40-hour work week. However, a significant proportion of the work force is employed in other work schedules. Any work schedule that incorporates more than 8 continuous hours, requires more than 5 consecutive days of work, or requires work during the evening or night, are considered *unusual* in this document. While the human body has adapted to the alternating day/night pattern which accompanies the approximately 24-hour rotation of the earth, unusual working hours may cause circadian disruption, sleep disorders, decreased performance and increased risk of health impairment.

Chemical exposures may obviously occur during usual as well as unusual working hours. Effects of chemical agents at the workplace may depend not only on exposure level and duration, but also on the time of exposure in relation to the circadian rhythm. However, practical experience regarding such combined effects is limited.

This document reviews the scientific support for a combined effect of unusual working hours and chemical exposure and compares different ways of adjusting the OEL to account for unusual working hours. Finally, a procedure for such adjustments is recommended.

2. Definition of unusual working hours

In Europe, the most common working hours is approximately 8 hours/day, 5 days/week, 48 weeks/year, for a working lifetime (up to 40 years) (98).

The European Foundation for the Improvement of Living and Working Conditions (Eurofound) has defined unusual working hours as:

- the extension of working hours through overtime,
- working at "unusual" times beyond traditional societal standards (such as the "09:00 to 17:00" norm), and
- varying time schedules over the week, month or year involving "changing" working hours (35).

The European Union Labour Force Survey (EU-LFS) categorises "atypical working time" in "evening or night work", "Saturday or Sunday working" and "shift work" (38).

According to the US Occupational Safety and Health Administration (OSHA), any shift that incorporates more than 8 continuous hours, requires more than 5 consecutive days of work, or requires work during the evening should be considered extended or unusual (86).

In this report, we categorise unusual working hours in shift work or extended working hours.

2.1 Shift work

Shift work can be classified in three types:

1) Permanent or rotating shift work – people work regularly on one shift only, or alternate more or less periodically on different shifts. Shift rotations are often classified as forward or backward rotating systems. A shift system that first moves from a morning shift to an evening shift and then to a night shift has a forward rotation (also called phase delayed or clockwise rotation). Counterclockwise rotation (night to evening to morning) is called backward rotation or phase advanced (71).

2) Continuous or discontinuous shift work – depending on whether all days of the week are covered or whether there is an interruption on weekends or on Sundays.

3) With or without night work – a night work shift schedule, is one where the working time is extended to all or part of the night. The number of nights worked can vary considerably. Moreover, the hours defined as night work vary from country to country, even between the Nordic countries (Table 1).

"Night time" is in the European Union (EU) defined as any period of not less than 7 hours, as defined by national law, and which must include in any case the period between midnight and 05:00. A "night worker" is (a) any worker who, during night time, works at least 3 hours of his/her daily working time as a normal course, and (b) any worker who is likely during night time to work a certain proportion of his/her annual working time, as defined at the choice of the Member State concerned, either by national legislation or by collective agreements (37).

Shift arrangements may also vary with regard to a variety of organisational factors, such as length and arrangement of a shift cycle (the length being the time, including both work shift and resting days, until the cycle is repeated), speed of shift rotation (the number of consecutive days worked in one shift type before changing), the number and distribution of rest days, and the regularity of the shift schedules. All of these factors may be combined in different ways, depending on the requirements specific to the profession. The three primary shifts are night shift,

Table 1. Definitions of night work and night work(ers) in the Nordic countries.

Country	Night time/night work	Reference
Denmark	*Night:* Unless otherwise agreed, the hours between 22:00 and 05:00. *Night work:* A time period of at least 7 hours, which includes the hours between midnight and 05:00.	(18)
Finland	*Night work*: Work carried out between 23:00 and 06:00. *Night shift*: At least 3 hours of duty between 23:00 and 06:00.	(106)
Norway	*Night work:* Work performed between 21:00 and 06:00.	(12)
Sweden	*Night:* Hours between 22:00 and 06:00. *Night worker:* A worker that performs at least 3 hours of his/her daily work during night time, or will probably perform at least 1/3 of his/her annual work during the night.	(10)

Table 2. Example of a 3-shift schedule for Norwegian nurses, with an average working week of 35.5 hours and a 12-week cycle (Oslo University hospital, HR-department).

Week	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Working hours
1		E	E			N	N	37
2	N							8
3	E	E	D	E	D			38.5
4	D	D				N	N	38
5	N		E	D	D			31.5
6	E	E	D	D	D			39
7	E	D	D		E	D	D	47
8		N	N	N				30
9	D	E	E	E	D			38.5
10	D	D	D		E	D	E	47
11	E		E	E	D			29
12	D	D	D	D	D			40

D: day/morning shift, E: afternoon/evening shift, N: night shift.

Table 3. Example of permanent night schedule for Norwegian nurses (Oslo University hospital, HR-department).

Week	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Working hours
1	N							7.75
2				N	N			20
3						N	N	22.25
4	N							7.75
5		N	N					20
6						N	N	22.25
7	N							7.75
8		N	N					20
9						N	N	22.25
10	N							7.75
11		N	N	N				30
12						N	N	22.25

N: night shift.

morning shift and evening shift. Examples of shift schedules among Norwegian nurses are given in Tables 2–3. Among nurses, permanent night work is less common than other shift schedules. Few nurses work full-time as permanent night workers. In Norway, permanent night work is most common at psychiatric units.

2.2 Extended working hours

In the present report, the term "extended working hours" is defined as work shifts longer than 8 hours. Extended work shifts may involve morning, evening or night shifts. "Compressed work weeks" means extended daily duty periods and normal weekly working hours. Potential benefits highlighted by adopting such a system, concern both employees (several consecutive days off, and less travel time between home and work), and third party (e.g. more continuity in therapist-patient relation). Some sectors follow shift schedules in which duration of both shifts and working

weeks are extended. In the Norwegian petroleum offshore industry, the most frequent arrangement consists of 2 weeks of work offshore, with shift duration of 12 hours all 14 days, and 4 weeks off. The most common alternatives for these shift rotation schedules are either fixed shifts of 14 consecutive day shifts or 14 consecutive night shifts, or a swing shift consisting of 1 week of night shifts followed by 1 week of day shifts on one tour, and day shifts followed by night shifts on the next tour (115).

A complicating factor in studying health effects of unusual working hours among offshore workers is that several factors influencing the diurnal rhythm in the fairly isolated work environment offshore differ significantly from the situation onshore (e.g. domestic duties and light exposure) (47, 115).

3. Occurrence of unusual working hours

The numbers in this chapter are based on data from the EU-LFS 1995–2021, which covers a representative sample of households in all 27 EU member states and in Iceland, Norway, Switzerland and the United Kingdom. The survey provides quarterly data on labour participation of people aged 15 years and over. The EU-LFS is conducted by national statistical institutes across Europe, using the same definitions of unusual working hours, according to the International Labour Organisation guidelines (40). The main findings in the four Nordic countries, are that Finland and Sweden have longer average *usual* working hours, whereas Denmark and Norway have shorter hours and the trend is declining (95).

3.1 Night work

The percentages of males and females aged 15–64 years working at night in the four Nordic countries combined are depicted in Figure 1. Overall, females perform night work to a lesser extent than males, while for both genders there is a declining trend over time (41). Also, there is a tendency to decreased gender gap (personal communication, Jouko Nätti, University of Tampere, Finland). Figure 1 shows that Finland had the highest percentage of employees usually working nights, and this was the case for both genders. In Denmark, the proportion of both female and male employees with night work seems to drop quickly in 2007 (41). Statistics Denmark states that they introduced a new way of calculating data of the Labour Force Survey in 2003 and 2007, and in 2007 additional information was drawn from several registers. In 2011, all register information is drawn from a specific register (103). The Swedish Labour Force Study was harmonised to EU standard around 2003–2005. Questions about working hours were altered by the introduction of a new questionnaire. The fact that time series analyses from Statistics Sweden begin in 2005 suggests that the changes observed between 2002 and 2004 regarding night work are probably due to new questions in the Labour Force Study (personal communication professor Lars Göran Kecklund, Dept. of Psychology, Stockholm University).

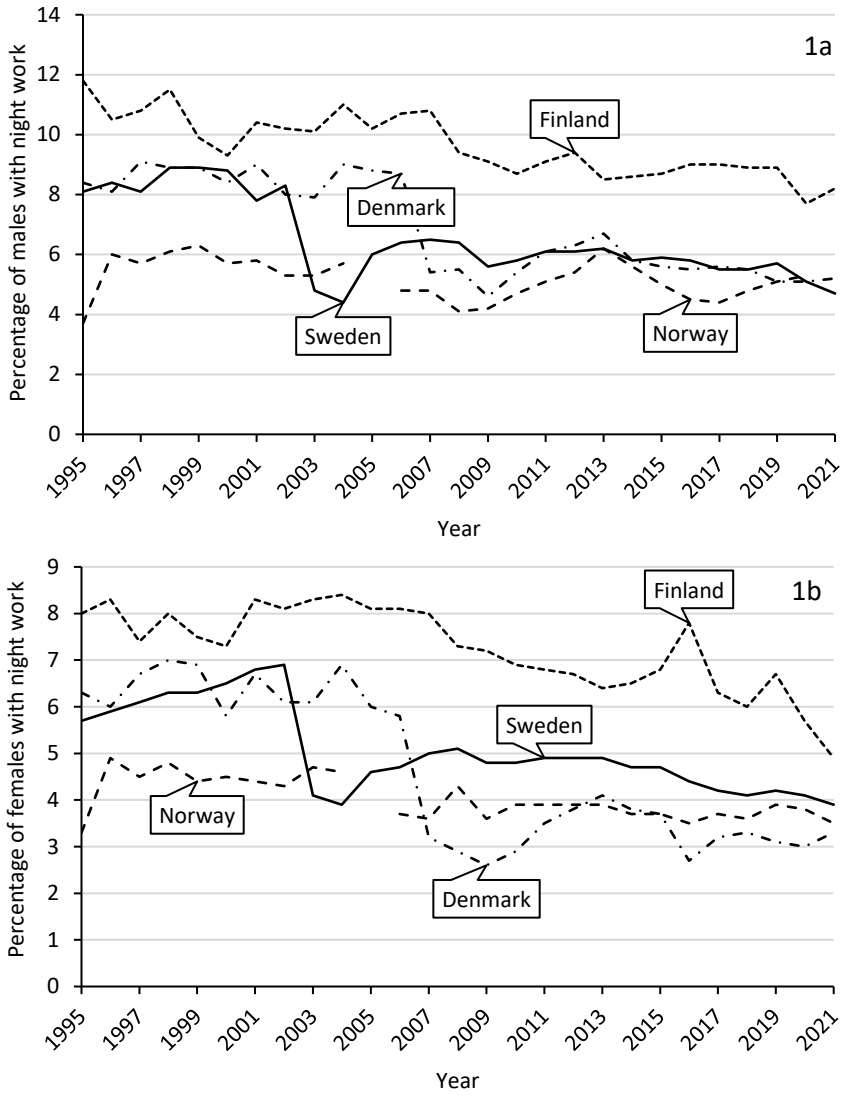

Figure 1. Percentage of male (a) and female (b) employees (aged 15–64 years) usually working at night by Nordic country and year (41). Number of participants in the survey in Denmark: 33 300, Finland: 36 400, Norway: 24 000 and Sweden: 45 700 (39).

Figure 2 shows the percentage of employees working night shift in various occupations in the Nordic countries. In spite of different definitions of shift work in the four countries, the percentages are rather similar. In all countries, the largest proportion of employees working night shift are found among the categories armed forces and unspecified (32–65%), plant and machine operators and assemblers (29–38%) and skilled agricultural and fishery workers (14–34%) (personal communication from Nordic4 by professor Jouko Nätti, University of Tampere, Finland).

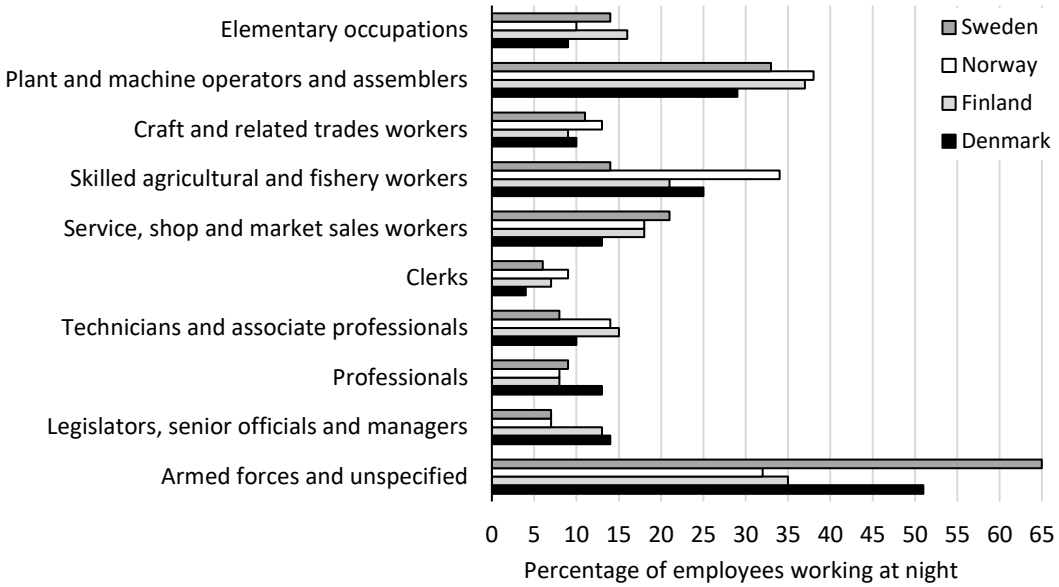

Figure 2. Percentage of employees in the Nordic countries working at night (usually or sometimes) year 2013, by occupation (ISCO1du). The figure is based on around 90 000 employees per country in the age range 15–64 years (personal communication from Nordic4 by professor Jouko Nätti, University of Tampere, Finland). Elementary occupations consist of simple and routine tasks which mainly require the use of hand-held tools and often some physical effort. ISCO: International Standard Classification of Occupations.

3.2 Extended working hours

The 6th European Working Condition Survey shows that it is predominantly men who work extended hours (21% men and 9% women usually work 48 hours or more per week, the definition of extended work hours in the survey), and that there are marked differences between countries regarding the proportion of workers working extended hours (36). This is also reflected in the EU-LFS data for the Nordic countries, as seen in Figure 3a and b. Among male workers (Figure 3a), the percentage of employees working extended hours declined from the year 2000 to 2020, in all four countries. The drop in Denmark around year 2007, should be interpreted with caution, as mentioned in relation to the figures of night work in Denmark (Section 3.1). During the whole period, the lowest proportion of male workers with extended working hours was found in Norway, and since 2007 the highest proportion was found in Finland. Also among female employees (Figure 3b) a decline in the proportion of employees with extended working hours was seen during the period for Finland, Denmark and Sweden. For female Norwegian employees the proportion kept more stable, around one percent, during the whole period, lower than for the other countries. For both women and men, the lowest percentages are found in Norway and Sweden (42).

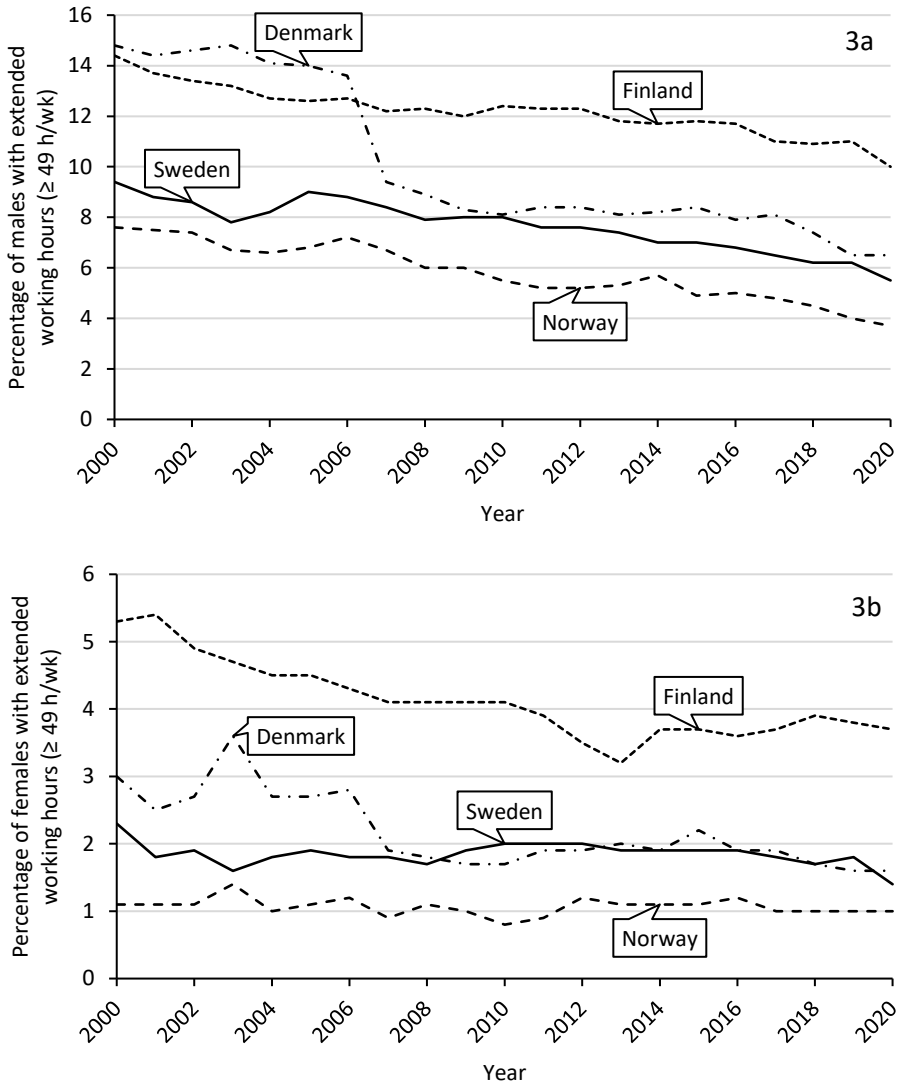

Figure 3. Percentage male (a) and female (b) employees (aged 15–64 years) usually having extended working hours (≥ 49 hours/week) by Nordic country and year (42). Number of participants in the survey in Denmark: 33 300, Finland: 36 400, Norway: 24 000, Sweden: 45 700 (39).

Figure 4 shows that in all the four Nordic countries extended working hours are most common among skilled agricultural, forestry and fishery workers. Extended working hours is also quite common among managers in Finland and Denmark, and in Finland also among plant and machine operators and assemblers.

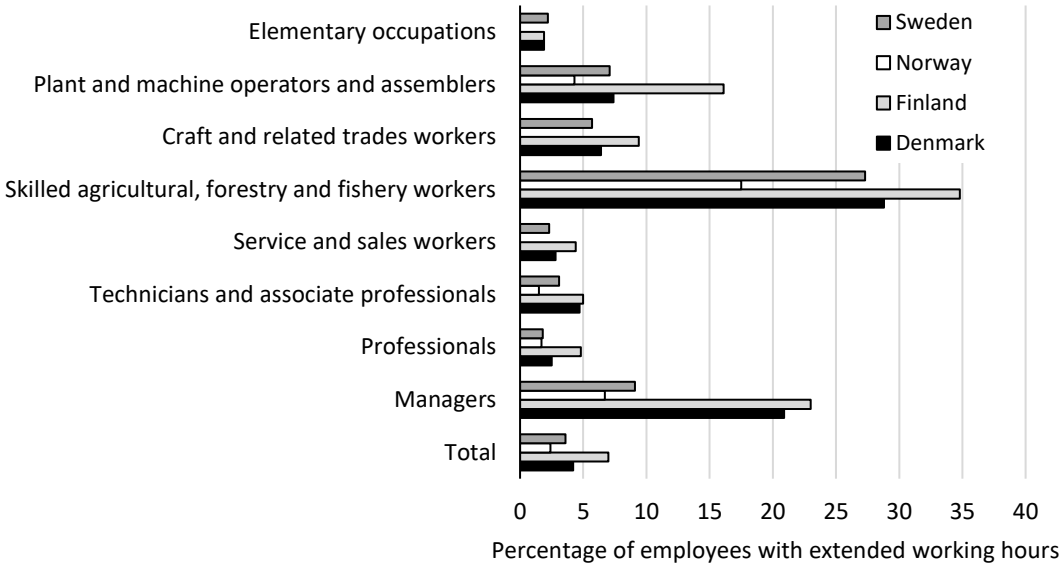

Figure 4. Percentage of employees (both sexes, aged 15–64 years) usually having extended working hours (≥ 49 hours/week) year 2020 by professional status and Nordic country (42).

3.3 Occupational exposure to chemicals in combination with shift work

Statistics on types of occupations and industries in which exposure to chemicals occurs in combination with unusual working hours are scarce. Figure 5 is based on the Norwegian Working Condition Survey, and shows the sectors with the highest percentage of workers reporting a combined exposure to chemical substances and night work. Among Norwegian workers as a whole, 19% of the male workers and 6% of the female workers reported that they can see or smell gas or vapour, or

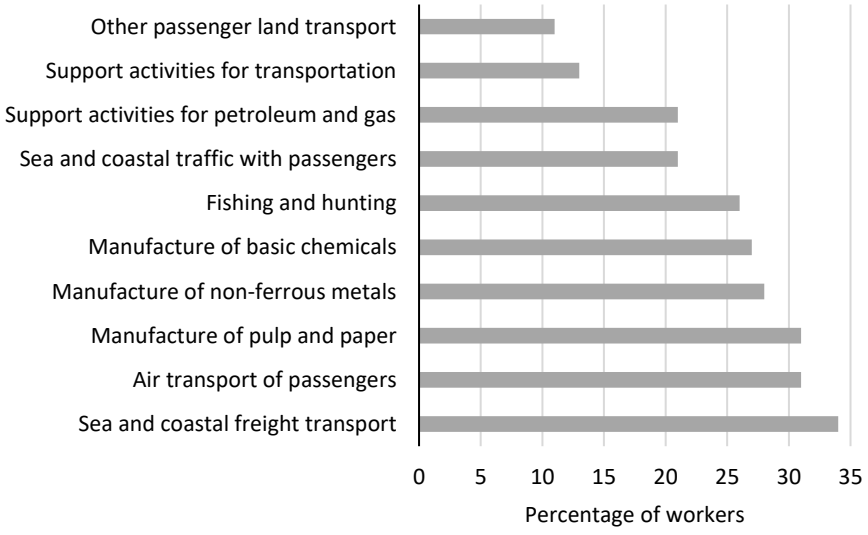

Figure 5. Percentage of Norwegian workers year 2013 with at least one night shift during the last 12 weeks who report that they can see or smell gas or vapour, or smell/inhale chemicals or chemical products at work at least a small part of the working time (104).

smell/inhale chemicals or chemical products at work at least a small part of their working time. Workers in sea and coastal freight transport, air transport of passengers and manufacture of pulp and paper are most exposed to the combination of chemicals and night work (104).

4. Mechanisms of adverse effects of chemical exposures and unusual working hours

4.1 Introduction

In combined exposure to chemicals and unusual working hours, adverse health effects may be a consequence of the chemical exposure alone (including exposure duration), the shift work alone, or a combination of both. The underlying biological mechanisms may also be operative for each factor alone or a combination of both risk factors. Plausible biological mechanisms common to both exposure factors are mainly those related to disruption of the circadian rhythm. Circadian rhythmicity has an important role in many physiological functions, including hormone levels, the immune system, lung function, cardiovascular system, activity of enzymes involved in metabolism and detoxification of chemicals, and tumour development. The hormone melatonin is central in the circadian rhythmicity (43, 109).

Melatonin is produced in the pineal gland and released in the blood stream in a circadian manner in response to information from photoreceptors in the retina mediated via the suprachiasmatic nucleus, the central circadian pacemaker. Melatonin is also produced in several other organs, but in these cases it is not secreted in blood and does not contribute to the circadian rhythmicity. Melatonin is involved in many functions, e.g. sleep initiation, mood modulation, sexual behaviour, vasomotor control, immune response, tumour inhibition and energy metabolism (43).

4.2 Hormonal disturbances

A synergistic effect of exposure to organic solvents and night work on spontaneous abortion was reported by Attarchi *et al.* (13). The underlying mechanisms are not clear, however, hormonal disturbances, arising either directly via impairment of circadian rhythms, or indirectly via sleep deprivation and psychosocial stress, are often mentioned in the literature (88).

4.3 Immune response

Melatonin is an important antioxidant and anti-inflammatory agent acting on several processes, including reduction or inhibition of oxidative stress, nuclear transcription factor kappa B (NFκB) and inflammasome NLRP3 (nucleotide-binding and oligomerisation domain-like receptor protein) activation, and inhibition of the pro-inflammatory cytokines (43).

4.4 Lung function

A decrease in lung function across night shift work (but not across daytime work) was reported when combined with exposure to zinc oxide dust (87). A possible mechanism for such a combined effect may be that lung function indices demonstrate a circadian rhythmicity, characterised by a lower tolerance at night (52). However, night shift alone has not been found to be associated with significant decreases in lung function (51), therefore exposure to zinc oxide might have an additive effect. Thus, exposure to high levels of zinc oxide dust combined with night shift work, appears to have strengthened the effect of circadian variation, possibly because of a narrowing of the airways, or because of an increased bronchial reactivity during the night. It is also possible that worsening may be related to the lower respiratory rate in the evening and night and that exposure to chemicals may further reduce the respiratory rate. An example is exacerbation of asthma during evening or night time, which is hypothesised to be related to the lower respiratory rate during evening and night (50).

4.5 Cardiovascular function

Orchestration of cardiac contractility, heart rate and blood pressure is important for normal physiological functioning of the cardiovascular system. These functions may be disturbed by shift work as well as by exposure to certain chemicals such as e.g. peroxynitrite that affects contractility (72). A review of evidence by Kecklund and Axelsson found that most of the studies showed an association between shift work and coronary heart disease. However, the authors could not rule out that this relationship might be due to biases in methodological problems such as inadequate confounder control, selection bias, and misclassification due to very crude measures of night work exposure (65). However, the combined effect of shift work, chemical exposure and coronary heart disease was not evaluated in this review.

When studying workers employed more than 90 days, an increased mortality due to coronary artery disease was observed in the group exposed to carbon disulphide and shift work for 4 years or more compared to workers with less than 4 years of these exposures (25).

4.6 Metabolic rate

Metabolism of chemicals in the body varies during the 24-hour cycle, enabling various organs in the body to respond and to adapt to environmental exposures and lifestyle factors. The liver is the major metabolising organ in the body and it has been estimated that 5–20% of its proteins may undergo oscillations during the 24-hour cycle due to fluctuations in exposure to environmental and lifestyle factors (16, 17, 32). Thus, night work likely leads to melatonin-mediated disruption of the circadian rhythm as well as changes in meal intake (66), both leading to metabolic oscillations in the liver that may affect detoxification rates and toxicity.

Mice injected with cadmium at different times showed a clear diurnal variation in mortality and liver and testis toxicity (78, 79, 82). The liver proteins glutathione *S*-transferase (GST) and metallothionein (MT), also shown to have a diurnal rhythm (19, 62, 117), were important factors for the cadmium toxicity. Chen *et al.* showed that the induction of fibrosis in the liver by carbon tetrachloride in mice may be related to alterations in the circadian rhythms of liver clock genes, where fibrotic liver glutathione (GSH) and MT levels are lower during daytime compared to non-fibrotic control livers. This may be due to decreased levels of peroxisome proliferator-activated receptor alpha (PPARα) and cytochrome P450 oxido-reductase (POR) proteins, which are circadian regulated (28).

4.7 Intestinal permeability

In two review articles it was proposed that alcohol (ethanol) disrupts central or peripheral (intestinal) circadian rhythms, resulting in increased permeability of the gut and leakage of bacterial endotoxins which reach the liver via the portal vein and cause an inflammatory response (46, 109). In combination with the ethanol metabolite acetaldehyde this may eventually lead to the various liver diseases (fibrosis, cirrhosis, fatty liver and liver cancer) related to heavy alcohol consumption. Later on, an experimental study with mice given a binge dose of ethanol (6 g/kg per day) for 3 days showed that ethanol increased intestinal permeability, and that the time of day of dosing affected the permeability as well as the degree of liver damage (steatosis, inflammation) (114).

4.8 Tumour promotion

Filipski and coworkers investigated the role of chronic jet-lag (CJL) as a tumour promoter in mice exposed to the liver carcinogen diethylnitrosamine (DEN). CJL mice showed increased growth of tumours and altered levels and circadian rhythms of proteins in the liver. The tumour suppressor protein 53 (p53) was downregulated while the tumour promoter c-Myc was upregulated (44).

5. Animal data

A number of animal experiments have been designed to mimic negative consequences of shift work in humans [reviewed in Opperhuizen *et al.* 2015 (83)]. Also, a large number of animal studies have dealt with chronopharmacological aspects of time of administration of drugs and sensitivity. These studies do not directly align with the present NEG document. However, there are no specific studies designed to assess the combined effects of unusual working hours and workplace relevant chemical exposure. Nevertheless, a few experimental animal studies were found that examined the combined effects of disturbance/disruption of circadian rhythm and chemical exposure. There are also a few animal studies that have compared the effects of a 12-hour repeated chemical exposure schedule with

those of an 8-hour schedule. Some of these studies are described below in Sections 5.1–5.2 and summarised in Tables 4–5.

5.1 Effects of combined exposure to chemicals and manipulated circadian rhythms

Filipski *et al.* investigated the combined effects of the liver carcinogen DEN and CJL in 44 male B6D2F$_1$ mice. The mice were given intraperitoneal doses of DEN during a 46-day period (total dose 243 mg/kg) and were subsequently randomised to either remain in the normal 12:12 hours light-dark cycle (LD12:12) or to undergo experimental CJL (8-hour advance of light onset every second day). CJL mice had higher plasma levels of aspartate aminotransferase (AST) than LD mice ($P = 0.005$) at 10 months. Liver tumours were seen in almost all DEN-treated mice after 10 months but CJL mice had more tumours per liver ($P = 0.03$), the mean diameter of the largest tumour was twice as large ($P = 0.03$) and up to 4 tumour types per liver were observed in the CJL mice, compared to 1 tumour type in the LD mice. Furthermore, DEN itself markedly disrupted the circadian rhythms during the LD12:12 regimen, measured by rest-activity and body temperature. This DEN-induced disruption was prolonged for ≥ 3 months by CJL exposure. The authors concluded that circadian disruption promotes liver carcinogenesis and possibly also contributes to the initiation (44).

Swiss female mice kept at LD12:12 (07:00/19:00, light during daytime) were administered a single topical application of a 0.1% solution of 7,12-dimethyl-benz[a]anthracene (DMBA) at 10:00 or 22:00. Applications of 5% croton oil to the exposed groups (75 animals/group) and the control group (50 animals) started one week later and were continued twice a week until 22 weeks after the first application. Mice painted at 22:00 had more papillomas (260 vs 161, $P = 0.01$) than those painted at 10:00 but there was no difference in the number of papilloma-bearing mice between the groups. The experiment was repeated once with same results (48).

Diurnal variation in susceptibility of epidermis to the tumourigenic action of 3-methylcholanthrene was studied in hairless mice kept in a room with natural light from the windows. A single dose of 125 µg 3-methylcholanthrene was applied to the dorsal skin at either 08:00 or 24:00 and the mice (25/sex/group) were followed for 20 months. No difference was found in tumour induction time or the number of papilloma-bearing mice. However, the group painted at 24:00 developed a higher number of skin papillomas (346 vs 258 papillomas, $P < 0.05$) and more animals had carcinomas/sarcomas (14 vs 7 animals), indicating that mice are more sensitive to 3-methylcholanthrene during night time (61).

Iversen and Iversen repeated the same experiment using larger groups of animals with slight variations in the applications times. The mice were painted with 125 µg 3-methylcholanthrene once at 12:00 or at 24:00 (48/sex/group) and followed for 20 months. There were no differences in tumour induction time, the number of papilloma-bearing mice or in the total number of papillomas or carcinomas between

the time groups. However among females, mice painted at 24:00 had more carcinomas (21 vs 14 animals, $P < 0.05$) than those painted at 12:00 whereas no such difference was found between the male groups (57).

Iversen *et al*. also studied circadian variation in hairless mice after a single topical application of 0.75 mg methylnitrosourea or 25 mg β-propiolactone at 12:00 or at 24:00 (74–76 animals/carcinogen and time group). The mice were kept at LD12:12 (06:30/18:30, light during daytime) and followed for 18 months. Mice painted at 12:00 with methylnitrosourea had slightly more skin tumours (papillomas + malignant skin tumours) than those painted at 24:00 (1.9 vs 1.7 tumours/animal, non-significant). Mice painted with β-propiolactone at 12:00 had significantly more skin tumours than those painted at 24:00 (1.0 vs 0 tumours/animal) (59). After applying new statistics tests the difference in tumour rate between animals painted with methylnitrosourea at 12:00 and at 24:00 was significant (ratio observed/expected 1.32 vs 0.72) (60).

In a study by the same research group, male and female hairless mice kept at LD12:12 (06:30/18:30, light during daytime) were administered a lower dose of methylnitrosourea (0.2 mg, a single dose that previously had been shown to not disturb the circadian rhythm of DNA synthesis and mitosis) to the dorsal skin once or three times with one week intervals at 08:00 or 20:00 (77–104 animals/time-point). The mice were followed for 18 months. The combined group painted (once + three times) at 20:00 had more papillomas and more papilloma-bearing mice than the combined group painted 08:00 (29).

In a later study by Iversen and Iversen, 638 hairless mice (50% females) kept at LD12:12 (7:30/19:30, light during daytime) were exposed by a single skin application to methylnitrosourea (1 or 2 mg) at different time-points and followed for 54 weeks. At 1 mg ($n = 351$), the percentage of tumour-bearing mice was higher in groups painted at 24:00, 04:00 or 08:00 than in those painted at 12:00, 16:00 or 20:00. Mice painted at 24:00 and 08:00 had also more tumours than those painted at other time-points. At 2 mg ($n = 287$), the percentage of tumour-bearing mice and the number of tumours were higher in groups painted at 20:00 or 08:00 than in the group painted at 12:00 (58).

In a few studies, the influence of injection timing on the toxicity of metals were studied in mice kept under standard condition i.e. LD12:12. Male ICR mice (5/group) were injected intraperitoneally with cadmium chloride ($CdCl_2$; 0 and 7.2 mg/kg, one shot) at different time-points (zeitgeber times (ZTs) 0, 4, 8, 12, 16 or 20; ZT0: light on, ZT12: light off) and mortalities were monitored until 14 days after the injection. Mice were sensitive to acute toxicity of Cd at the light phase (ZT8), while tolerant at the dark phase (around ZT20). Likewise, the hepatic GSH levels in non-treated mice were lowest at ZT8 and highest at ZT20. In contrast, hepatic MT levels (the protein that bind to Cd) were not correlated to the Cd-induced mortality (79).

In a similar study by the same authors, male C57BL/6J mice (5/group) received a single intraperitoneal injection of 6.4 mg/kg $CdCl_2$ at ZTs 2, 6, 10, 14, 18 or 22 or of 4.5 mg/kg $CdCl_2$ at ZTs 6 or 18. All mice injected with 6.4 mg/kg at ZT2 died

within the 14-days observation period whereas those injected at ZT18 survived. In mice injected with the non-lethal dose of 4.5 mg/kg, the activities of alanine aminotransferase (ALT) and AST in plasma (collected 2–24 hours after injection) were markedly increased 24 hours after injection at ZT6 whereas these values were mostly unchanged in mice injected at ZT18. These diurnal variations in Cd-sensitivity were not correlated to differences in hepatic Cd level, basal hepatic GSH or MT levels or Cd-induced hepatic MT levels. Cd-induced hepatic GSH levels were reduced 6 hours after injection at ZT6 but not at ZT18. Buthionine sulphoximine given in drinking water for 4 days (to deplete the GSH) before the Cd-injection abolished the diurnal variation in ALT and AST. According to the authors, this suggested a contribution of GSH to Cd-induced chronotoxicity (78).

In another study by the same research group, testicular toxicity was studied in male C57BL/6J mice injected with a single intraperitoneal dose of 4.5 mg/kg $CdCl_2$ (4/group) at ZT6 or ZT18 and sacrificed 7 days after the injection. Sperm head numbers and sperm motility were reduced at ZT6 injection compared to the control group, but no significant changes were observed at ZT18 injection. Similar results were observed in mice subcutaneously injected once with 4 or 6 mg/kg $CdCl_2$ (6–8/group) and sacrificed 10 days after dosing. The results indicated that the testicular toxicity of Cd is influenced by the injection timing (82).

The same research group also investigated lethal chronotoxicity of seven other metal compounds (nickel, chromium, copper, zinc, mercury, lead, iron) in male ICR mice. The mice were injected intraperitoneally with a single dose of each metal compound at ZTs 2, 6, 10, 14, 18 or 22 (5/group) and mortality was followed until 14 days after injection. Mice were tolerant against nickel toxicity at ZTs 18 and 22 (dark phase) but susceptible to chromium at ZTs 10–22. The toxicities of copper and zinc were most pronounced in the time zone during which light and dark were reversed (ZTs 10, 14). The chronotoxicity of mercury and lead seemed to be biphasic with two peaks [survival number of mice were higher at ZTs 6–10 (light) and 22 (dark) for mercury, and at ZTs 10 (light) and 18 (dark) for lead], whereas no diurnal variation in toxicity was observed for iron. Thus, chronotoxicity was recognised for all the metals except iron (119).

Yoshioka *et al.* also investigated whether bromobenzene toxicity varies by circadian periodicity. Male ICR mice kept at LD12:12 were injected intra-peritoneally with bromobenzene once, with 900 mg/kg at ZTs 0, 6, 12, or 18 (6/group) or with 540 mg/kg (non-lethal dose) at ZTs 6 or 18 (6/group). Mice were sensitive to the bromobenzene-induced mortality (monitored for 7 days) at ZT6 and more tolerant at ZT18. Thus, the number of surviving mice was 0/6 for the ZT6 condition and 2/6 for ZT18, whereas the mean survival times were 0.5 and 3.5 days, respectively. Likewise, mice injected with the non-lethal dose at ZT6 had markedly increased plasma levels of ALT and AST, more pronounced hepatic lipid peroxidation and histopathological liver damage than those injected at ZT18 (118).

Chen *et al*. studied the impact of fibrogenesis on the hepatic circadian system in male C57BL/6 mice maintained in LD12:12. Liver fibrosis was induced by intraperitoneal injections of 0.6 ml/kg bw carbon tetrachloride (CCl_4) diluted in

olive oil twice a week for 4 weeks and a control group received the same volume of vehicle. The mice (5–6/group) were sacrificed 1 day after the last injection at ZTs 1, 5, 9, 13, 17 and 21. Liver fibrosis led to alterations in the hepatic circadian expression of several clock genes (*clock, Bmal1, Per1, Cry1* and *Cry2*), but not of *Per2*. The expression of *Cry2* was completely disrupted in the fibrotic livers during daytime (ZTs 1, 5 and 9). Also, the clock-regulated genes, *PPARα* and *POR* lost circadian rhythm with severely declined hepatic mRNA levels during daytime (28).

Bruckner *et al.* investigated whether the hepatic metabolic activation of CCl_4 was rhythmic and coincided in time with maximum susceptibility to CCl_4 hepatotoxicity and if lack of food during the sleep cycle resulted in formation of acetone. Acetone is involved in the induction of cytochrome P4502E1 (CYP2E1) in the liver, resulting in increased metabolic activation of CCl_4 and acute liver injury. Groups of fed and fasted male Sprague Dawley rats (6/group) acclimated to LD12:12 were given a single dose of 0 or 800 mg/kg bw of CCl_4 by gavage at 2- to 4-hour intervals over a 24-hour period and were sacrificed 24 hours after the dosing. Serum enzymes (ALT, sorbitol dehydrogenase (SDH), isocitrate dehydrogenase) activities measured 24-hour post-exposure and used as indices of hepatotoxicity exhibited pronounced circadian rhythms in both fed and fasted animals dosed with CCl_4 with distinct maxima near the beginning of their dark/active cycle (ZT18). Fasted animals were more sensitive than fed ones. Serum enzyme activities did not vary significantly in untreated rats. Pretreatment of fed rats with diallyl sulphide (a CYP2E1 inhibitor, peroral dose of 20 mg/kg) 12 hours before CCl_4-treatment blocked the CCl_4 hepatotoxicity and abolished the diurnal rhythm in susceptibility. Blood acetone, hepatic CYP2E1 activity, and covalent binding of $^{14}CCl_4$ metabolites to hepatic microsomal proteins in untreated rats followed circadian rhythms similar to that of susceptibility to CCl_4. Parallel fluctuations of greater amplitude were seen in fasted rats. Hepatic GSH levels were lowest at the time of greatest susceptibility to CCl_4. Acetone dose-response experiments showed high correlations between blood acetone levels, CYP2E1 induction, and CCl_4-induced liver injury. The results support a role for acetone in induction of CYP2E1 and for CYP2E1 in modulating the chronotoxicity of CCl_4 in rats (24).

Wang *et al.* investigated whether acute ethanol-induced liver injury and fatty liver exhibit circadian variations consistent with hepatic expression of *Per* genes. Male C57BL/6 mice, wild type (WT) or lacking *Per1* (*Per1-/-*) or *Per2* (*Per2-/-*) genes, were maintained under LD12:12. In the 1st experiment, WT mice were given a single oral dose of ethanol (5 g/kg bw) at ZT1 or ZT13 and sera and livers were collected 6 hours after the dosing. Mice dosed at ZT1 were less susceptible to ethanol-induced liver injury as indicated by lower ALT and AST levels and less liver injury. The circadian fluctuation of acute ethanol-induced liver toxicity was consistent with circadian pattern of *Per1* and *Per2* expression (hepatic mRNA levels peaked at ZT13 and troughed at ZT1). In the 2nd experiment, WT, *Per1-/-* and *Per2-/-* mice received ethanol (5 g/kg bw) by oral gavage every 12 hours for a total of 3 doses. Serum and liver were collected 10 hours after the last dose. *Per1-/-* mice were less susceptible to ethanol-induced liver injury (lower serum

ALT and AST levels and less severe liver injury) than WT and *Per2-/-* mice. Deletion of *Per1* prevented ethanol-induced triglyceride synthesis by supressing elevations of gene expression of PPARγ and its target genes related to triglyceride synthesis, leading to reduced hepatic lipid accumulation in response to ethanol. These results indicate that circadian rhythms of ethanol-induced liver toxicity are controlled by the clock gene *Per1*, and deletion of *Per1* protected mice from ethanol-induced liver injury by decreasing hepatic lipid accumulation (116).

In another study, effects of chronic ethanol exposure on the liver of *Clock*-mutant (*Clock+/-*) mice were investigated. WT and *Clock+/-* mice maintained on LD12:12 were given water or 15% ethanol for 8 weeks and then sacrificed at ZTs 0, 6, 12 or 18 (4 mice/group). Ethanol in the drinking water increased the liver weight in *Clock+/-* mice and the hepatic triglyceride levels in both *Clock+/-* and WT regardless time of day, but this lipid accumulation was larger in the *Clock+/-* mice. Ethanol also altered the expression in the liver of genes involved in lipid metabolism in *Clock+/-* mice, but did not alter expression of circadian clock genes in either *Clock+/-* or WT mice. According to the authors, this indicates that disruption of circadian rhythmicity associated with the mutation in the *Clock* gene could be a risk factor for the development of an alcoholic fatty liver due to exposure to ethanol (73).

Perreau-Lenz *et al.* studied diurnal variation in ethanol sensitivity in male C57BL/6N mice (WT, *Per1-/-* or *Per2-/-*) maintained under LD12:12. In the 1st experiment, WT mice were given a single intraperitoneal injection of ethanol (3.5 g/kg bw) at ZTs 5, 11, 17 or 23 and loss of righting reflex (LORR) duration, also known as the labyrinthine righting reflex, was measured immediately after the injection. In a parallel experiment, the elimination rate of ethanol was assessed in blood samples collected 30, 60 and 240 minutes after ethanol injection at same time-points. WT mice displayed diurnal variation in LORR duration, with the longest duration at ZT11, i.e. after exposure to ethanol late in the light cycle. The ethanol elimination rates did not differ between the different time-points. In a similar experiment with the clock-mutant mice injected at ZTs 5 and 11, *Per1-/-* mice demonstrated similar diurnal pattern as WT mice. In contrast, *Per2-/-* mice did not exhibit diurnal variation in LORR duration, revealing a constant high sensitivity to ethanol (92).

Diurnal variations in intestinal barrier integrity and liver pathology were investigated in male C57BL6/J mice kept at LD12:12. The mice were fed a standard chow diet with or without ethanol (4.5% vol/vol) for 4 weeks. Subsequently, the mice received a single dose (i.e. binge) by gavage for 3 consecutive days of ethanol (6 g/kg bw) or vehicle control at ZTs 0, 4, 8, 12, 16 or 20. After the 2nd binge, the mice (fasted overnight) were given a solution with non-absorbable, poorly digestible sugars (lactulose, mannitol, sucrose, sucralose) and urine was collected for 5 hours. Four hours after the final binge the animals were euthanised and blood and liver samples collected. Terminal body weight, serum ethanol, markers of intestinal permeability [urinary lactulose, mannitol, sucrose, sucralose, and serum lipopolysaccharide (LPS) and LPS-binding protein (LBP)] and markers of liver

pathology [steatosis, inflammation, liver myeloperoxidase (MPO), serum ALT and AST] were analysed. A high level of sugar in the urine is an indication of intestinal hyperpermeability. Only sucralose (a marker of whole intestine and colonic permeability) demonstrated a significant effect of time and also showed a binge by time interaction, suggesting that the time of alcohol binge influences colonic permeability. The alcohol binge-induced intestinal barrier dysfunction was greatest when the binge was administered at ZT0 (114).

In summary, although the animal studies described above have not been designed and optimalised for combined effects of unusual working hours and chemical exposures, they suggest that the time of exposure (day-night) may affect the biotransformation and toxicity of chemicals. It is also noted that the most relevant and important occupational exposure route is inhalation while the studies described above have used other exposure routes.

5.2 Effects of repeated chemical exposure for more than 8 hours per day

Paustenbach and coworkers studied the effects of exposure duration and repeated inhalation exposure to carbon-14 labelled carbon tetrachloride ($^{14}CCl_4$) on the toxicokinetics and adverse effect. Male Sprague Dawley rats (4/group) were repeatedly exposed to 100 ppm for 8 hours during 10 days or for 11.5 hours during 7 days (total exposure was 800 ppm-hour in both cases). Toxicokinetic analyses were made using a two-compartment model and were based on measurement of ^{14}C activity in exhaled air. The kinetic analysis indicated that there were no significant differences in mean or peak plasma concentrations of CCl_4. However, the second (beta phase) half-time was longer in rats exposed for 11.5 hours (496 ± 32 min), compared to 8 hours (400 ± 32 min), suggesting a higher build-up in fat tissues. This interpretation was also supported by a higher percentage exhaled $^{14}CCl_4$ and a lower percentage excreted ^{14}C in urine and faeces (presumably mainly metabolites). Overall, there were no significant differences in mean or peak plasma levels of $^{14}CCl_4$ (91, 112). Histopathology revealed no differences in hepato- or nephro-toxicity between the two regimes. However, the 11.5-hour exposure resulted in significantly higher serum SDH (indicator of liver damage) activity, compared to the 8-hour exposure (90).

Kim *et al*. exposed male Sprague Dawley rats to 10, 30, 50 or 150 ppm aniline during 8 hours for 5 days or during 12 hours for 4 days (5/group). At 50 and 150 ppm, methaemoglobin (metHb) levels increased more in the 12-hour regimen group compared to the 8-hour regimen group, both at the end of exposure and next morning. No consistent difference between the two regimens were seen at 30 ppm. No elevation of metHb was seen in either regimen at 10 ppm (70).

Kim *et al.* also studied carboxyhaemoglobin (COHb) resulting from inhalation exposure of male Sprague Dawley rats and Swiss Webster mice to 200, 500 and 1 000 ppm dichloromethane (DCM) using the same exposure design (5/group). No difference in COHb formation was seen between the 8-hour and 12-hour exposures (69).

Table 4. Effects in animals of combined exposure to chemicals and manipulated circadian rhythms.

Strain, species and no. of animals per sex	Chemical exposure	Circadian condition (LD12:12 unless otherwise specified)	Results	Reference
B6D2F$_1$ mice, 44 males	Diethylnitrosamine (DEN), 7–10 mg/kg/d by 30 i.p. injections during a 46-d period at ZT11 (total dose 243 mg/kg).	Mice submitted to CJL (1 d after the last injection) or remained in LD12:12.	CJL mice had higher plasma levels of AST than LD mice at 10 mo. Almost all mice had liver tumours after 10 mo but CJL mice had more tumours per liver, larger tumours and up to four tumour types per liver compared to one tumour type in LD mice. DEN itself induced disruption of the circadian rhythms (suppressed rest-activity and body temperature rhythms) in both CJL and LD mice, but the disruption was prolonged for ≥ 3 mo by CJL exposure.	(44)
Swiss mice, 75 females per time group and 50 controls	7,12-Dimethylbenz[a]-anthracene (DMBA), 0.1% by single skin application followed by repeated application of 5% croton oil.	LD12:12 (07:00/19:00) [a] *Time of dosing* 10:00 or 22:00, followed for 22 weeks.	Mice painted 22:00 had more papillomas than those painted 10:00 (260 vs 161, P=0.01). No difference in number of papilloma-bearing mice between exposed groups. The experiment was repeated once with same results.	(48)
Hairless mice, 25 males and 25 females per time group	3-Methylcholanthrene, 125 µg by single skin application	Natural light-dark cycle *Time of dosing* 08:00 or 24:00, followed for 20 mo.	Mice painted 24:00 had more papillomas (346 vs 258, $P < 0.05$) and more animals had carcinomas/sarcomas (14 vs 7). No difference in number of papilloma-bearing mice between the two exposed groups.	(61)
Hairless mice, 48 males and 48 females per time group	3-Methylcholanthrene, 125 µg by single skin application	Natural light-dark cycle *Time of dosing* 12:00 or 24:00, followed for 20 mo.	Females painted 24:00 had more carcinomas than those painted 12:00 (21 vs 14, $P < 0.05$) than those painted 12:00. No difference in the number of papilloma-bearing mice or in total number of papillomas/carcinomas between the exposed groups.	(57)

Table 4. Effects in animals of combined exposure to chemicals and manipulated circadian rhythms.

Strain, species and no. of animals per sex	Chemical exposure	Circadian condition (LD12:12 unless otherwise specified)	Results	Reference
Hairless mice, 74–76 per time group and chemical (sex not given)	Single skin application of: 0.75 mg methylnitrosourea	LD12:12 (06:30/18:30) [a] *Time of dosing* 12:00 or 24:00, followed for 18 mo.	Mice painted 12:00 had slightly had more skin tumours (papillomas + malignant skin tumours) than those painted 24:00 (1.9 vs 1.7 tumours/animal, non-significant). After applying new statistics tests the difference in tumour rate between animals painted 12:00 and 24:00 was significant (ratio observed/expected 1.32 vs 0.72).	(59, 60)
	25 mg β-Propiolactone		Mice painted 12:00 had significantly more skin tumours than those painted 24:00 (1.0 vs 0 tumours/animal).	
Hairless mice (50% males), 77–104 per time group	Methylnitrosourea, 0.2 mg by skin application once or three times with one week intervals	LD12:12 (06:30/18:30) [a] *Time of dosing* 08:00 or 20:00, followed for 18 mo.	The combined group painted (once + three times) 20:00 had more papillomas and more papilloma-bearing mice than the groups painted 08:00.	(29)
Hairless mice (50% males), 351; 32–159 per time group	Methylnitrosourea, single skin application of: 1 mg	LD12:12 (07:30/19:30) [a] *Time of dosing* 04:00, 08:00, 12:00, 16:00, 20:00 or 24:00, followed for 54 wk.	The percentage of tumours-bearing mice was higher in groups painted 24:00, 04:00 or 08:00 than in those painted 12:00, 16:00 or 20:00. Mice painted 24:00 and 08:00 had also more tumours than those painted at the other time-points.	(58)
287; 32–128 per time group	2 mg	08:00, 12:00 or 20:00, followed for 54 wk.	The percentage of tumours-bearing mice was higher in groups painted 20:00 or 08:00 than in those painted 12:00. Mice painted 20:00 and 08:00 had also more tumours.	

Table 4. Effects in animals of combined exposure to chemicals and manipulated circadian rhythms.

Strain, species and no. of animals per sex	Chemical exposure	Circadian condition (LD12:12 unless otherwise specified)	Results	Reference
ICR mice, 5 males per dose and time group	$CdCl_2$, single i.p. injection: 0 and 7.2 mg/kg	*Time of dosing* ZTs 0, 4, 8, 12, 16 or 20, followed for 14 d.	Mice were sensitive to Cd-induced mortality at ZT8 while tolerant at around ZT20. Likewise, the hepatic GSH levels in non-treated mice were lowest at ZT8 and highest at ZT20. In contrast, the hepatic MT levels were not correlated to the Cd-induced mortality.	(79)
C57BL/6J mice, 5 males per dose and time group	$CdCl_2$, single i.p. injection: 6.4 mg/kg	*Time of dosing* ZTs 2, 6, 10, 14, 18 or 22, followed for 14 d.	6.4 mg/kg: All mice injected at ZT2 died, whereas those injected at ZT18 survived.	(78)
	0 or 4.5 mg/kg (non-lethal dose)	ZTs 6 or 18	4.5 mg/kg: Increased activities of ALT and AST in plasma 24 h after injection at ZT6 but not at ZT18. Hepatic GSH levels reduced 6 h after injection at ZT6 but not at ZT18. Hepatic MT levels were similar after injection at ZT6 and ZT18.	
	20 nM Buthionine sulphoximine in drinking water		Buthionine sulphoximine given to deplete GSH for 4 d before the Cd-injection abolished the diurnal variation in ALT and AST.	
C57BL/6J mice, 4 males per dose and time group	$CdCl_2$, single injection: 0 or 4.5 mg/kg (i.p.)	*Time of dosing* ZTs 6 or 18	Reduced sperm head numbers and sperm motility 1-wk after injection at ZT6 compared to the control group, but no significant changes were observed at ZT18.	(82)
6–8 males per dose and time group	0, 4 or 6 mg/kg (s.c.)	ZTs 6 or 18	Reduced sperm head numbers (at ZT6 but not at ZT18 at 4 mg/kg, at both ZTs at 6 mg/kg); and reduced sperm motility at ZT6 at 6 mg/kg), compared to controls, evaluated 10 days post-injection.	

Table 4. Effects in animals of combined exposure to chemicals and manipulated circadian rhythms.

Strain, species and no. of animals per sex	Chemical exposure	Circadian condition (LD12:12 unless otherwise specified)	Results	Reference
ICR mice, 5 males per chemical and time group	Single i.p. injection, mg/kg $K_2Cr_2O_7$: 61.5 $CuCl_2$: 9.5 $NiCl_2$: 42.75 $ZnCl_2$: 53.9 $FeCl_2$: 130 $HgCl_2$: 12.8 or $(CH_3COO)_2Pb \times 3 \times H_2O$: 277	*Time of dosing* ZTs 2, 6, 10, 14, 18 or 22, followed for 14 d.	Chronotoxicity (mortality) was recognised for all the metals except Fe. Mice were tolerant against Ni-toxicity at ZTs 18 and 22 but susceptible to Cr at ZTs 10–22. The toxicities of Cu and Zn were most pronounced at ZTs 10 and 14, whereas the chronotoxicity of Hg and Pb seemed to be biphasic [survival number of mice were higher at ZTs 6–10 (light) and 22 (dark) for Hg, and at ZTs 10 (light) and 18 (dark) for Pb].	(119)
ICR mice, 6 males per dose and time group	Bromobenzene, single i.p. injection: 0 or 900 mg/kg	*Time of dosing* ZTs 0, 6, 12 or 18, followed for 7 d.	Mice were sensitive to the bromobenzene-induced mortality (monitored for 7 days) at ZT6 and more tolerant at ZT18. Thus, the number of surviving mice was 0/6 for the ZT6 condition and 2/6 for ZT18, whereas the mean survival times were 0.5 and 3.5 days, respectively.	(118)
	0 or 540 mg/kg (non-lethal dose)	ZTs 6 or 18, sacrificed 18 h later.	Mice injected at ZT6 had markedly increased plasma levels of ALT and AST, and more pronounced hepatic lipid peroxidation and histopathological liver damage than those injected at ZT18.	

Table 4. Effects in animals of combined exposure to chemicals and manipulated circadian rhythms.

Strain, species and no. of animals per sex	Chemical exposure	Circadian condition (LD12:12 unless otherwise specified)	Results	Reference
C57BL/6 mice, 5–6 males per dose and time group	CCl_4, 0 or 0.6 ml/kg bw by i.p. injection 2 d/wk for 4 wk	*Time of sacrifice* ZTs 1, 5, 9, 13, 17 and 21, 1 d after last injection.	Liver fibrosis induced by CCl_4 led to alterations in the hepatic circadian expression of several clock genes (*Clock, Bmal1, Per1, Cry1 and Cry2*), but not for *Per2*. The mRNA expression of *Cry2* was totally disrupted, with markedly reduced levels during daytime (ZT1, ZT5 and ZT9).	(28)
Sprague Dawley rats (fed or fasted), 6 males per dose and time group	CCl_4, 0 or 800 mg/kg bw by single oral gavage Predosing: Diallyl sulphide, 20 mg/kg bw orally (fed rats) Acetone, 0, 50, 100, 250, 500, 1 000, or 2 000 mg/kg bw by single oral gavage (fed and fasted)	*Time of dosing* 2- or 4-h intervals over 24 h, sacrificed 24 h after dosing.	Serum enzyme (ALT, SDH, ICD, measure of hepatotoxicity) activities exhibited pronounced circadian rhythms in both fed and fasted exposed animals with distinct maxima near the beginning of dark/active cycle. Fasted animals were more sensitive than fed ones. Predosing of fed rats with diallyl sulphide (a CYP2E1 inhibitor) blocked the CCl_4 hepatotoxicity and abolished the diurnal rhythms in susceptibility to the injury. Blood acetone and hepatic CYP2E1 activity in fed and fasted control rats followed circadian rhythms similar to that of susceptibility to CCl_4 toxicity, with fluctuations of greater amplitude in fasted rats. Blood acetone levels correlated to CYP2E1 induction and CCl_4-induced liver injury (i.e. SDH activity), respectively. The findings show acetone's physiological role in CYP2E1 induction and the role of CYP2E1 in modulating CCl_4 chronotoxicity in rats.	(24)

Table 4. Effects in animals of combined exposure to chemicals and manipulated circadian rhythms.

Strain, species and no. of animals per sex	Chemical exposure	Circadian condition (LD12:12 unless otherwise specified)	Results	Reference
C57BL/6 WT mice, 5 males per dose and time group	Ethanol, single oral gavage 0 or 5 g/kg bw	*Time of dosing* ZTs 1 or 13, sacrificed 6 h later.	WT mice dosed at ZT1 had lower ALT and AST levels and less liver injury than WT mice dosed at ZT13. The circadian fluctuation in ALT and AST was consistent with hepatic expression of *Per1* and *Per2*.	(116)
C57BL/6 WT, *Per1*-/- and *Per2*-/- mice, 5 males per strain, dose and time group	0 or 5 g/kg bw	Every 12 h for a total of 3 doses, sacrificed 10 h later.	*Per1*-/- mice had lower serum ALT and AST levels and less severe liver injury than WT and *Per2*-/- mice. Deletion of *Per1* prevented ethanol-induced triglyceride synthesis by supressing elevations of expression of PPARγ and its target genes related to triglyceride synthesis, leading to reduced hepatic lipid accumulation in response to ethanol.	
ICR WT and *Clock*+/- mice, 4 females per strain and time group	Ethanol, 0 or 15% ethanol via drinking water for 8 wk.	*Time of sacrifice* ZTs 0, 6, 12 or 18	Increased liver weight in *Clock*+/- mice and increased hepatic triglyceride levels in both *Clock*+/- and WT mice regardless time of sacrifices, but the lipid accumulation was larger in the *Clock*+/- mice. Altered expression in the liver of genes involved in lipid metabolism in *Clock*+/- mice, but no altered expression of circadian clock genes in either *Clock*+/- or WT mice.	(73)

Table 4. Effects in animals of combined exposure to chemicals and manipulated circadian rhythms.

Strain, species and no. of animals per sex	Chemical exposure	Circadian condition (LD12:12 unless otherwise specified)	Results	Reference
C57BL/6N WT mice, 11–26 males per time group	Ethanol, single i.p. injection 3.5 g/kg bw	*Time of dosing* ZTs 5, 11, 17 or 23, evaluated immediately after injection.	WT mice displayed diurnal rhythm in LORR duration (CNS sensitivity), peaking at ZT11, but showed no differences in elimination rates of ethanol between the different time-points.	(92)
C57BL/6N WT, *Per1* ^{BRDM1} and *Per2* ^{BRDM1} mice, 8–18 males per strain and time group	3.5 g/kg bw	ZTs 5 or 11, evaluated immediately after injection.	*Per1* ^{BRDM1} mice displayed similar diurnal pattern as WT mice, with enhanced LORR duration at ZT11. In contrast, *Per2* ^{BRDM1} mice showed no diurnal variation in LORR, revealing a constant sensitivity to ethanol.	
C57BL6/J mice, 5–10 males per dose and time group	Mice fed a standard chow diet with or without ethanol (4.5% vol/vol) for 4 wk were given 0 or 6 g/kg bw (binge) ethanol by gavage for 3 consecutive days in wk 5	*Time of dosing* ZTs 0, 4, 8, 12, 16 or 20 Intestinal permeability evaluated after 2nd binge.	Sucralose (a marker of whole intestine and colonic permeability) demonstrated a significant effect of time and also showed a binge by time interaction, suggesting that the time of alcohol binge influences colonic permeability. The alcohol binge-induced intestinal barrier dysfunction was greatest when the binge was administered at ZT0.	(114)

[a] Light during daytime.

ALT: alanine aminotransferase, AST: aspartate aminotransferase, Bmal: brain and muscle Arnt-like protein, CCl_4: carbon tetrachloride, $CdCl_2$: cadmium chloride, CJL: chronic jet-lag (8-hour advance of light onset every 2nd day), CNS: central nervous system, Cry: cryptochrome, CYP: cytochrome P450, DEN: diethylnitrosamine, GSH: glutathione, ICD: isocitrate dehydrogenase, i.p.: intraperitoneal, LD12:12: 12:12 hours light-dark cycle, LORR: loss of righting reflex, MT: metallothionein, Per: period, PPAR: peroxisome proliferator-activated receptor, s.c.: subcutaneous, SDH: sorbitol dehydrogenase, ZT: zeitgeber time (ZT0 = light on; ZT12 = light off), WT: wild type.

Table 5. Effects in animals of repeated chemical exposures for more than 8 hours per day.

Strain, species and no. of animals	Chemical exposure	Exposure duration	Results	Reference
Sprague Dawley rats, 4 males per time group	$^{14}CCl_4$ inhalation: 100 ppm	8 h/d for 10/12 d or 11.5 h/d for 7/12 d, i.e. essentially the same dose (8 000 ppm-h) for both schedules.	11.5-h group compared to 8-h group: Longer second (beta) elimination half-time suggesting a slightly higher build-up in fat tissues, higher percentage exhaled $^{14}CCl_4$ and lower percentage excreted ^{14}C in urine and faeces. No significant differences in mean and peak plasma levels of $^{14}CCl_4$, nor in hepato- and nephrotoxicity. Significantly higher SDH activity, an indicator of liver damage.	(90, 91, 112)
Sprague Dawley rats, 5 males per dose and time group	Aniline inhalation: 0, 10, 30, 50 or 150 ppm	8 h/d for 5 d or 12 h/d for 4 d	12-h group compared to 8-h group: 10 ppm: No elevation of metHb in the groups. 30 and 50 ppm: No consistent difference in metHb between the groups. 150 ppm: Increased metHb both at the end of exposure and next morning.	(70)
Sprague Dawley rats and Swiss Webster mice; 5 males per dose and time group	DCM inhalation: 200, 500 and 1 000 ppm	8 h/d for 5 d or 12 h/d for 4 d	No difference in COHb formation between the 8-h and 12-h groups.	(69)

CCl_4: carbon tetrachloride, COHb: carboxyhaemoglobin, DCM: dichloromethane, metHb: methaemoglobin in blood, SDH: sorbitol dehydrogenase.

6. Human data

6.1 Procedure of article evaluation and relevance grading of studies

The latest literature search was made in 2021 (for details see Chapter 13), and articles were included if i) exposure to both chemicals and shift work/extended working hours was defined, and ii) outcome (health or safety) was defined. The included articles were then evaluated according to the following *relevance categories*:

> Relevance category 1: Shift work/extended working hours is defined in line with Chapter 2 in this document. Measures of chemical exposure may be quantitative or qualitative (exposed vs unexposed). Effects are presented as biomarker levels and/or health effects. Statistical analyses, including risk estimates of the combined exposure to unusual working hours and chemical exposure are reported.
>
> Relevance category 2: As for relevance category 1, however risk estimates from statistical analyses are not reported.

Studies of both categories are summarised in Table 6 (shift work) and Table 7 (extended working hours). The most informative studies (Relevance 1) are described in more detail in the following sections.

6.2 Shift work

6.2.1 Reproductive effects

In 2010, Attarchi *et al.* performed a cross-sectional study of women in reproductive age, employed in a pharmaceutical factory in Teheran, Iran, to evaluate the correlation between occupational chemical exposures and spontaneous abortions and time to pregnancy. Women working in the laboratory units and exposed to chemicals (n = 205, mean age 32.1 years, 22% on shift work) were compared to women working in the packing units and considered unexposed (n = 201, mean age 31.4 years, 30% on shift work). Data were collected through a direct interview, including questions concerning a number of life-style factors, medication usage, duration of chemical exposure in the current job, working hours and history of pregnancy. Information about spontaneous abortions (defined as a pregnancy that ended before 20 weeks of gestation) was confirmed by medical records. The cut-point for prolonged time to pregnancy was 12 months. The mean concentrations of formaldehyde, phenol, *n*-hexane and chloroform (personal sampling) in the five laboratory units were 0.01, 0.5, 20.7 and 3.2 ppm, respectively. A total exposure was estimated by calculating a "hazard index" (HI), assuming additivity and using the American Conference of Governmental Industrial Hygienists (ACGIH) 2008 threshold limit values (TLVs) (1). The HI values ranged from 0.55 to 0.93. The frequency of spontaneous abortion was higher in laboratory workers than in

unexposed (10.7% vs 3.0%; odds ratio (OR) 3.90, 95% confidence interval (CI) 1.54–9.85), and higher in shift workers than in daytime workers (12.1% vs 5.01%; OR 2.68, 95% CI 1.20–5.71). When combining work schedule and chemical exposure the ORs (95% CI) for spontaneous abortion were 4.10 (1.69–9.93) for shift work and no chemical exposure, 5.40 (2.02–14.4) for daytime work and chemical exposure, and 13.5 (5.28–34.6) for shift work and chemical exposure (all compared to daytime work and no chemical exposure). Thus, a synergistic effect on spontaneous abortion was found between shift work and occupational chemical exposure. Also the proportion of women waiting ≥ 12 months to become pregnant was higher among laboratory workers than among packing unit staff (14.1% vs 7.0%; OR 2.20, 95% CI 1.26–4.30). Using logistic regression analysis, a dose-response relationship was observed for spontaneous abortion with ORs (95% CI) increasing from 5.21 (1.95–14.1) in the low-exposed group (HI 0.55–0.87) to 7.70 (2.09–15.4) in the high-exposed group (HI > 0.87), after adjustment for age at pregnancy, work experience and shift work. Corresponding ORs (95% CI) for time to pregnancy increased from 2.76 (1.15–4.21) to 4.48 (1.89–8.43) (13). Although the exposure was expressed as HI and included chemicals with different critical effects, the study provides some support for a combined effect of chemical exposure and shift work.

6.2.2 Cardiovascular disease

Carreón *et al*. updated the mortality data of 1 874 (1 739 men) workers employed for 1 day or more at a chemical manufacturing plant in US 1946–2006. Exposures to vinyl chloride, carbon disulphide (CS_2), shift work, and categories of *o*-toluidine exposure were reassessed, and based on year, department and job title. The plant was operated 24 hours/day, 7 days/week, and numerous workers worked in a rotating shift schedule. All workers assigned to the rubber chemicals department 1954–1994 were considered as exposed to CS_2 but also some jobs assigned to other departments including the polyvinyl chloride (PVC)-vinyl department were considered CS_2 exposed. In all, 67% of the workers were classified as exposed ≥ 1 day to CS_2 and many of them had also performed shift work. For CS_2 exposure, coronary artery disease mortality was not associated with duration of employment. Internal comparisons showed increased coronary artery disease mortality among workers exposed to both CS_2 and shift work for ≥ 4 years (standardised rate ratio (SRR) 2.70, 95% CI 1.05–6.93) compared to those exposed for 90 days to < 4 years. Mortality was not higher among workers with ≥ 4 years of just one of these exposures. The authors suggested that CS_2 and shift work may be cofactors in the presence of other risk factors (25). The study provides support for a combined effect of CS_2 exposure and shift work.

A Belgian cross-sectional health survey included 115 male viscose rayon workers exposed to CS_2 (66% with rotating shift work) and 76 referents not exposed to this chemical (86% with rotating shift work). The participants were interviewed using the World Health Organization (WHO) cardiovascular questionnaire and responded to a self-administered questionnaire. Electrocardiogram (ECG) and blood pressure

were recorded and blood lipoproteins determined. Personal monitoring performed in 17 jobs showed exposures to CS_2 varying from 4 to 112 mg/m^3. For each individual a CS_2 cumulative exposure index was calculated. The prevalences of angina, history of myocardial infarction, intermittent claudication and ECG signs of ischaemia were similar in exposed and referents. Systolic and diastolic blood pressure, and some lipoparameters (low density lipoprotein (LDL)-cholesterol and the apolipoproteins A1 and B) rose while other (high density lipoprotein (HDL)-cholesterol, HDL-cholesterol/apolipoprotein A1 and LDL-cholesterol/apolipo-protein B ratios) decreased significantly with increasing exposure. Total cholesterol and triglycerides were not significantly changed. Multiple linear regression analysis revealed an association between CS_2 cumulative exposure index and blood pressure (both systolic and diastolic) and all lipoparameters except triglycerides after adjustment for age, body mass index, smoking, alcohol consumption, stress and tension at work, shift work, noise exposure and educational level. Shift work was not related to any of these outcomes, as indicated by non-significant regression coefficients (110). The study provides no support for a combined effect of shift work and CS_2 exposure on the cardiovascular outcomes.

6.2.3 Respiratory diseases

Nemery *et al.* investigated across-shift lung function indices in 25 steelworkers from a dusty strandcasting department and in 11 comparable steelworkers exposed to considerably lower dust levels, over an almost uninterrupted 21-days working period and over three different work shifts. The average total dust exposure in the strandcasting department was 11.8 mg/m^3 (personal sampling) and in the control area 1.7–1.8 mg/m^3 (stationary sampling). All subjects were examined at the beginning, in the middle, and at the end of their first (day 1) morning shift, their last (day 14) afternoon shift, and their last (day 21) night shift. Lung function changes were not significant in either group over the morning shift. During the afternoon shift, there were significant decreases in spirometric indices in the casting group, but not in the control group, however the interactions between exposure and time were generally not significant. The decreases across the night shift were more pronounced in the casting group than in the control group; forced expiratory volume in 1 second (FEV_1) 3.0% vs 1.1%, FEV_1/vital capacity (FEV_1/VC) 2.3% vs 0.8% and forced expiratory flow between 25% and 75% of VC ($FEF_{25–75}$) 7.7% vs 1.0%. The authors concluded that the more pronounced decrease in spirometric indices, suggestive of slight airway obstruction, found over the night shift in the strand-casting workers was due to the work environment (80). The study provides support for a combined effect of shift (night) work and dust exposure on lung function.

Pasker *et al.* examined lung function in steel plant workers of which 57 were exposed to zinc oxide fumes and 55 were non-exposed (controls). Most of the participants worked in shifts over a period of 21 days, with shift changes every 7 days. Lung function measurements were performed at the beginning and near the end of a work shift (day or night) and were repeated 1 day later. The average total dust concentrations were 8 (1.0–22.8) mg/m^3 (personal sampling) and the respirable

zinc oxide was on average 5.1 mg/m^3. During the day shift, there were no significant differences in lung function between exposed and control workers. VC and FEV_1 decreased slightly both in exposed and non-exposed workers. During the night shift, VC, FEV_1 and slope of respiratory resistance (R_{rs}) decreased significantly in exposed, but not in controls. However, there was no significant difference in the change between exposed and controls. The study provides some support for a combined effect of shift (night) work and zinc oxide exposure on lung function (87).

Relationships between endotoxin exposure, work-related respiratory symptoms, and acute peak flow changes were studied in 97 shift workers from four potato-processing plants in the Netherlands. Peak expiratory flow (PEF) was measured daily for a 23-day period and across-shift changes in PEF were determined for morning, afternoon, and night shifts. Endotoxin exposure was assessed based on plant and job category, and ranged from 53 to 8 167 endotoxin units per m^3 (EU/m^3). PEF increased across the morning shift (+2.7%) and decreased across the afternoon (-1.3%) and night shifts (-1.7%). These patterns in peak flow change in the different shifts were consistent with expectations, on the basis of the circadian rhythm. A higher endotoxin exposure was associated with a smaller PEF increase across the morning shift and a larger PEF decrease across afternoon and night shifts as well as with an increased prevalence of work-related symptoms. The effect related to endotoxin exposure was significantly higher for the afternoon shift than for the morning and night shifts (120). The study indicates a combined effect of shift work and endotoxin exposure.

6.2.4 Sleep disorders

Kiesswetter *et al.* investigated if solvent exposure alone (experimental chamber study) or combined solvent exposure and shift work (field study) influence sleep. The quality of sleep was recorded after the period of sleep via a questionnaire. In the chamber study, 16 healthy, male subjects (20–30 years) were exposed for 4 hours (09:00–13:00) at weekly intervals to air (control), 1 000 ppm acetone, 400 ppm ethyl acetate, and a mix of 500 ppm acetone and 200 ppm ethyl acetate in random order, and subjective estimates of night-time sleep following each exposure were investigated. Night-time sleep durations did not differ significantly between the four groups, but significantly deeper sleep was reported under all solvent exposure conditions in comparison to the control conditions. The field study included 16 healthy male 3-shift workers from a cellulose acetate manufacturing plant of which 8 subjects were exposed to an average concentration of 980 ppm acetone and 8 subjects were unexposed (controls). Workers were on a rapidly rotating shift system, having three consecutive shifts (morning, afternoon, night) each week. Measurements were undertaken for three weeks. During the shifts, acetone concentration was monitored in the air of the breathing zone and in the urine (both in two 4-hours periods). Dose-response relationships were found between acetone in air and urine during the three different work shifts and sleep quality. The exposed shift workers reported a reduced sleep recovery, mainly in connection with daytime sleep, in comparison with non-exposed shift workers. At

night, the exposed shift workers fell asleep relatively quicker. For daytime sleep, they reported a relatively low "depth of sleep" and "low recovery". Interaction effects between night shift and acetone exposure were found for recovery ($P = 0.005$) and trends were found both for falling asleep and depth of sleep ($P < 0.1$) (68). The study indicates some support for a combined effect of acetone exposure and night shift work.

6.2.5 Other health outcomes

Kiesswetter *et al.* studied neurobehavioral effects of shift work and solvent exposure. All study participants were healthy males on 2-shift work (morning and afternoon shift with weekly rotation) or 3-shift work (short rotated morning, afternoon and night shift cycles with 1 day free in between). The 2-shift study included 8 subject exposed to mixed solvents from printing colours and cleaning agents and 8 matched unexposed controls from the same company. Personal exposure measurements indicated that 3/15 detected solvents exceeded 25% of the German maximum workplace concentrations (MAKs) whereas 12 were clearly below the MAKs. The 3-shift study included 8 subjects exposed to acetone-soaked filters and 8 matched controls who worked in a "clean air" area in the packing department. The average acetone concentration across all shifts was close to 1 000 ppm and 30% of the 123 personal samples collected exceeded the MAK (1 000 ppm at that time). Ratings of well-being (tension, tiredness, complaints, annoyance) and acute symptoms (discomfort, irritation, difficulties in breathing) and scoring of performance (simple reaction time, colour word vigilance) were performed at the beginning, middle and end of each shift. For 2-shift mixed solvent exposed workers, tension and tiredness ratings deviated more from controls during the morning shift that during the afternoon shift (chemical exposure × shift). Across-shift trends differed from controls only in reaction time and annoyance (exposure × across shift). Across shifts, the 3-shift (acetone-exposed) workers had an increase in adverse effects ($P < 0.1$) in all measured variables (acetone × across shift). Tiredness and colour word vigilance trends (across shift), differed more during morning shift than during the other two shifts, although the acetone-exposed group revealed the highest values of tiredness during the night shift. Both exposure to acetone and shift work contributed to the stronger adverse effects under the 3-shift condition (67). The study indicates some support for a combined effect of exposure to mixed solvents or acetone and shift work.

6.3 Extended working hours

6.3.1 Biomarkers of exposure

Shih *et al.* investigated if carbon disulphide (CS_2) accumulates after a 1-week exposure period, and how the duration and exposure magnitude of two different work shifts affects this accumulation, for workers in viscose rayon industry (Table 7). The study included 6 CS_2-exposed subjects on 8-hour shift, 7 CS_2-exposed subjects on 12-hour shift and 7 unexposed control subjects. Personal air monitoring

in the breathing zone covered full work shifts. Urine was collected pre- and post-shift every day for 5 consecutive days. 2-Thiothiazolidine-4-carboxylic acid levels in the urine (U-TTCA), a biomarker for exposure to CS_2, were determined. The CS_2 exposure levels for a 12-hour shift (arithmetic mean ± standard deviation 11.3 ± 1.47 ppm) were significantly greater than for an 8-hour shift (6.3 ± 0.64 ppm). The authors concluded that accumulation of U-TTCA occurs for prolonged shifts (12-hour), but not for the normal, 8-hour shift. The U-TTCA accumulation was exposure-magnitude-dependent (100). NEG analysed these field data in more detail by fitting the half-time of U-TTCA (one-compartment model) to the CS_2 and U-TTCA data in Shih *et al*. (100). This analysis confirmed that the difference in pre-shift as well as post-shift U-TTCA values between the 8-hour and 12-hour shift workers is well explained by differences in exposure level (magnitude) and exposure duration (G Johanson, personal communication) and with the same half-time (8.5 hours) in both groups. Thus, the study provides no support for a combined effect of CS_2 exposure and extended working hours.

Table 6. Studies on shift work and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Shift work	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
Reproductive effects						
Cross-sectional study *Cohort:* 205 female workers in 5 laboratory units (20–40 y of age) employed ≥ 1 y in a pharmaceutical factory, Tehran, Iran. *Referents:* 201 female workers employed ≥ 1 y in 2 packing units (20–40 y of age) in the same factory. Study performed 2010.	*Personal sampling, mean concentrations (ppm)* Formaldehyde: 0.01 Phenol: 0.5 *n*-Hexane: 20.7 Chloroform: 3.2. Total exposure expressed as HI, assuming additivity and using 2008 TLVs. HIs were 0.55–0.93; in low- and high-exposed ≤ 0.87 and > 0.87, respectively.	*Personal interviews* Daytime or shift work (fixed evening, fixed night or rotating). *Exposed* Daytime: 77.5% Shift work: 22.5%. *Referents* Daytime: 70% Shift work: 30%.	*Spontaneous abortion, OR (95% CI)* Chemically exposed vs referents 3.90 (1.54–9.85) (all, crude) 5.21 (1.95–14.12) (low-exposed, log regression) 7.70 (2.09–15.38) (high-exposed, log regression) Shift workers vs daytime workers 2.68 (1.20–5.71) (all, crude) 4.13 (1.70–10.0) (all, log regression) Chemically exposed and/or shift work vs referents 1.00 (ref. no chemical exposure, daytime work) 4.10 (1.69–9.93) shift work only 5.40 (2.02–14.4) chemical exposure only 13.5 (5.28–34.6) chemical exposure + shift work *Time to pregnancy > 12 mo, OR (95% CI)* Chemically exposed vs referents 2.20 (1.26–4.30) (all, crude) 2.76 (1.15–4.21) (low-exposed, log regression) 4.48 (1.89–8.42) (high-exposed, log regression) Shift workers vs daytime workers 2.85 (1.11–4.36) (all, log regression)	Adjustment for age at pregnancy and work experience.	(13)	Some support for a combined effect of chemical exposure and shift work [1]

Table 6. Studies on shift work and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Shift work	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
Cohort: 2 146 women, born in 1940 or later and members of the Swedish Midwives Association in 1989, and with pregnancies that started 1980–1987 and ended in single births. 1 781 pregnancies linked to 1 302 women who worked > 20 h/wk during the second trimester of pregnancy.	*Self-administered questionnaire* Frequency of use of N_2O when assisting deliveries Never: 53% < 50%: 21% ≥ 50%: 26%.	*Self-administered questionnaire* Extent of work Full time: 53% Part time: 47% Work schedule Daytime: 23% Night work: 13% 2-shift: 47% 3-shift: 16%.	Work schedule and N_2O use were correlated, because daytime work was most common in antenatal care, and 3-shift was mainly practiced in delivery wards. *N_2O use* Reduced birth weight -77 g (95% CI -129– -24) Increased risk of infants being SGA (≤ 10^{th} percentile of weight) OR 1.8 (95% CI 1.1–2.8) *Night work* Preterm birth (< 37 wk) OR 5.6 (95% CI 1.9–16.4) when adjusted for N_2O use. Associations between night work and preterm birth became more pronounced when N_2O use was entered into the model. This information was given in the discussion only, and no effect estimates were provided. Linear and logistic regression.	Adjustment for maternal age, parity, and employment.	(21)	Insufficient information for evaluation of a combined effect of N_2O exposure and night work [2]

Table 6. Studies on shift work and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Shift work	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
Cohort: 3 358 women, born 1940 or later and members of the Swedish Midwives Association in 1989. Of the 1 484 most recent pregnancies which terminated after 1983, 1 023 were planned, and 972 of these were included. The analysis was restricted to women who had worked > 20 h/wk during the conceiving period.	*Self-administered questionnaire* Frequency of N_2O use when assisting deliveries Average no. of deliveries/mo: 0: 48% 1–10: 22% 11–20: 19% 21–30: 6% > 30: 6%.	*Self-administered questionnaire* Extent of work Full time: 47% Part time: 53% Work schedule Daytime: 25% Night work: 13% 2-shift: 42% 3-shift: 19%.	*Fecundability ratio (95% CI)* Night/shift work vs daytime work Only nights 0.82 (0.65–1.04) 2-shift 0.78 (0.65–0.94) 3-shift 0.77 (0.61–0.98) N_2O deliveries vs no N_2O deliveries > 30 deliveries/mo using N_2O 0.63 (0.43–0.94). Discrete time-analogue of the Cox proportional-hazards model.	Adjustment for age, cycle order, pregnancy order, previous fertility problem, oral contraceptive use, and tea consumption.	(3)	Insufficient information for evaluation of a combined effect of N_2O exposure and shift work [2]

Table 6. Studies on shift work and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Shift work	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
Cohort: 1 587 women, born 1940 or later and members of the Swedish Midwives Association in 1989, who had worked as midwife > 20 h/wk during their first trimester, with a total of 1 717 pregnancies 1980–1988.	*Self-administered questionnaire* Frequency of use of N_2O when assisting deliveries Never: 35% ≤ 50%: 29% > 50%: 36%.	*Self-administered questionnaire* Extent of work Full time: 47% Part time: 53% Work schedule Daytime: 25% Night work: 17% 2-shift: 37% 3-shift: 22%.	*Spontaneous abortion, OR (95% CI)* Night/shift work vs daytime work Night work 1.63 (0.95–2.80) 2-shift 1.16 (0.73–1.84) 3-shift 1.49 (0.86–2.59) N_2O use vs no N_2O use ≤ 50% 0.75 (0.48–1.19) > 50% 0.95 (0.62–1.47) *Late spontaneous abortions (> 12th wk of pregnancy), OR (95% CI)* Night/shift work vs daytime work Night work 3.33 (1.13–9.87), 17 cases 2-shift 1.11 (0.42–2.94) 3-shift 0.71 (0.20–2.48) N_2O use vs no N_2O use ≤ 50% 1.02 (0.41–2.53) > 50% 1.05 (0.44–2.52) Logistic regression. *Interaction effects* Not included in the models in the final analyses as their contribution to the goodness of fit was negligible.	Adjustment for calendar year, age, previous spontaneous abortion, smoking, infection and shortage of staff.	(14)	Insufficient information for evaluation of a combined effect of N_2O exposure and shift work [2]

Table 6. Studies on shift work and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Shift work	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
Cross-sectional study *Cohort:* 745 women (1 160 pregnancies) born in 1935 and later, engaged in laboratory work 1968–1979 at the University of Gothenburg, Sweden.	*Self-administered questionnaire* Exposure to various solvents, during the first trimester and later in pregnancy.	*Information from payrolls* Day work or shift work (unspecified).	*Outcome of pregnancy* Solvent exposure during pregnancy No differences in perinatal death rates or prevalence of malformations compared to infants of unexposed mothers. Shift work during pregnancy Miscarriage: RR 3.19 (95% CI 1.36–7.47) Shift work and solvent exposure Shift work increased the miscarriage rate among those unexposed to solvents ($P < 0.0001$). Mantel-Haenszel procedure.	Pregnancies during shift work excluded when testing for the relation between work with solvents and miscarriage frequency during the first trimester.	(15)	Insufficient information for evaluation of a combined effect of solvent exposure and shift work [2]
Case-control study *Cases:* 255 men, having their first appointment for infertility evaluation at an Egyptian hospital (mean age 30.1 ± 6.2 y). *Controls:* 267 fertile men (29.9 ± 6.1 y). Study performed 2008–2009.	*Self-administered questionnaire* Occupational exposure last month: Solvents and painting materials (12.2% vs 3.4% in controls), lead (7.1% vs 1.1%), pesticides, gasoline, welding or soldering fumes, mineral oils or wax, printing materials, anaesthetic gases.	*Self-administered questionnaire* Presence of shift work: 8.2% vs 2.6% in controls.	*Infertility (OR, 95% CI)* Solvents & painting materials 3.88 (1.50–10.03) Lead 5.43 (1.28–23.13) Shift work 3.60 (1.12–11.57) Multivariable logistic regression.	Adjustment for smoking and BMI.	(34)	Insufficient information for evaluation of a combined effect of chemical exposure and shift work [2]

Table 6. Studies on shift work and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Shift work	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
Cohort: 3 946 pregnant women (1 865 included in analysis) in West Germany 1987–1988, recruited in gestational wk 15–28.	*JEM* Weighted for no. of working h/wk. Exposure categorised as no, low, moderate or high, and included organic solvents, carbon tetrachloride, herbicides, chloro-phenols, poly-chlorinated biphenyls, aromatic amines, lead and lead compounds, mercury and mercury compounds.	*Self-administered questionnaire* on occupational factors, but no details on shift work provided.	*SGA, P(trend)* Dichotomous logistic regression analysis (yes/no) Chlorophenols P = 0.02 Aromatic amines P = 0.05 Polytomous logistic regression analysis Mercury P = 0.01 (limited study power). Further adjustment for income, shift work and heavy physical work had no substantial effect on the results.	Adjustment for age, smoking status, alcohol consumption, BMI and number of former births.	(99)	Insufficient information for evaluation of a combined effect of chemical exposure and shift work [2]
Cross-sectional study *Cohort:* 44 men (aged 20–57 y; mean age 37) employed in a US chemical plant that manufactured 4,4'-diamino-stilbene-2,2'-disulphonic acid (DAS), an intermediate used for the production of optical brightening agents.	*Personal sampling* 19 samples, 24% had detectable levels of PNTSA, 38% of DNS and 1 sample had detectable levels of DAS. All exposures were near the detection limits (~10 µg/m^3 for DNS and PNTSA).	*Work schedules* Rotating shift: 39 Daytime: 5.	*Symptoms* (reported since beginning work in the production area over the preceding ≥ 6 mo) Impotence 14% Decreased libido 36% *Serum testosterone* Low levels (< 350 ng/dl) 37% (not fully accounted for by diurnal variation or an effect of rotating shift work, i.e. exposure to chemicals possessing oestrogenic activity may be related to the effect).		(94)	Insufficient information for an evaluation of a combined effect of chemical exposure and shift work [2]

Table 6. Studies on shift work and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Shift work	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
Exposure also to *p*-nitrotoluene sulphonic acid (PNTSA), dinitro-stilbene-2,2'-disulphonic acid (DNS).	DNS and DAS have structural similarities to diethylstilbestrol (DES), a synthetic oestrogen. Evidence also for potential dermal exposure.					
Cross-sectional study *Cohort:* 907 pregnant working women receiving prenatal care at two hospitals in Thailand. Retrospective data collection conducted March–November in 1995.	*Personal interviews* Exposure to paints, varnish, lacquer, dyes, pigments, inks, solvents, welding fumes, insecticides, herbicides, wood preservative agents, anaesthetic gas, X-ray films or radioactive agents. *Exposure groups* 1: 2–3 times/wk or most of time. 0: occasionally or never (dominating choice).	*Personal interviews* Rotating shift, fixed afternoon shift or fixed night shift.	*Shift work* No association. Logistic regression.	Adjustment for age, education, BMI, menstrual regularity, obstetric and medical history, coital frequency, and potential exposure to reproductive toxic agents (yes/no), but the impacts of the respective confounders were not analysed.	(108)	Insufficient information for evaluation of a combined effect of chemical exposure and shift [2]

Table 6. Studies on shift work and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Shift work	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
Cross-sectional study Cohort: 8 904 nurses and 3 977 non-nurse health care workers in China. Study of relationship between occupational hazards and menstrual disorders with data collection in 2016. 41% of nurses and 32% of non-nurses experienced menstrual disorders.	Personal interviews on occupational activities; Handling of disinfectant (yes/no) and handling of anti-cancer drug (yes/no).	*Personal interviews* Night work vs day work, rotating shift work vs day work and overtime work (yes/no).	*Overall menstrual disorders, OR (95% CI), univariate analyses* Handling disinfectant 1.93 (1.79–2.08) Handling anti-cancer drug 1.66 (1.48–1.87) Night work vs. day work 1.31 (1.19–1.43) Rotating shift vs. day work 1.37 (1.26–1.49) Overtime work 1.26 (1.17–1.36) *Multiple regression* Irregular menstrual cycles associated with handling disinfectants, night work and overtime work. Dysmenorrhea associated with handling disinfectants, anti-cancer drugs and rotating shifts. No analyses of interaction effects between exposures.	Adjustments for age, marital status, children, workload, noise, prolonged standing and heavy lifting.	(63)	Insufficient information for an evaluation of a potential combined effect of exposure to disinfectants and anti-cancer drugs and shift work [2]

Table 6. Studies on shift work and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Shift work	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
Cardiovascular diseases						
Cohort: 1 874 workers (93% males) employed ≥ 1 d 1946–2006 in a chemical manufacturing plant, New York, US, of which 67% were exposed to carbon disulphide (CS_2). *Referents:* US mortality rates (SMR) or internal comparison (SRR).	Exposure to CS_2 in the rubber chemicals department 1954–1994. No exposure estimates were given.	The plant operated 24 h/d, 7 d/wk, and numerous workers were in a forward rotating shift work schedule.	*Coronary artery disease mortality (employment ≥ 90 d* , SRR (95% CI) Exposure to CS_2 and shift work ≥ 4 y vs < 4 y No shift work or CS_2 1 Only CS_2 1.10 (0.57–2.10) Only shift work 1.41 (0.77–2.60) Shift work + CS_2 2.70 (1.05–6.93)		(25)	Support for a combined effect of CS_2 exposure and shift work [1]
Cross-sectional study *Cohort:* 115 male workers (median age 34.0 y) exposed to carbon disulphide (CS_2) and employed for ≥ 1 y at a viscose rayon factory in Belgium. *Referents:* 76 unexposed male workers (median age 33.5 y) in a metal-works, a plastics factory and a starch processing factory.	*Personal monitoring (17 jobs)* 4–112 mg/m^3. Individual CS_2 cumulative exposure indexes were calculated ("low" or "high"). Working conditions had not changed since 1932.	*Self-administered questionnaire* Rotating shift work: Exposed: 66.1% Unexposed: 85.6%.	Cardiovascular effects *CS_2-exposure* No significant effects on the prevalence of angina, history of myocardial infarction, intermittent claudication and ECG signs of ischaemia. Significant effects of the CS_2 index (multiple linear regression analysis) Systolic and diastolic blood pressure ↑ Apolipoproteins A1 and B ↑ Cholesterol, LDL-cholesterol ↑ HDL-cholesterol ↓ HDL-cholesterol/apolipoprotein A1 ratio ↓ LDL-cholesterol/apolipoprotein B ratio ↓ *Shift work* No significant impact on the associations.	Adjustment for age, BMI, smoking, alcohol consumption, stress and tension at work, shift work, noise exposure and educational level. As expected, age was a determinant of many of the outcomes, but shift work was not related to any of the lipids.	(110)	No support for a combined effect of CS_2 exposure and shift work [1]

Table 6. Studies on shift work and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Shift work	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
Respiratory diseases						
Cohort: 25 steelworkers (mean age 33.1 y) from a strandcasting department in Belgium. *Referents:* 11 steel-workers (mean age 34.8 y) not exposed to dust, but working according to the same shift schedule.	*Air sampling, mean total dust*, mg/m^3 Exposed: 11.8 (0.5% soluble fluoride), personal. Referents: 1.7 and 1.8 (0.05% fluoride), stationary. *Post-shift urinary fluoride* was higher among exposed, but did not vary between day and night shifts.	21 consecutive workdays, 3-shift; 7-day shifts: morning (06–14) → 7 days afternoon (14–22) → 7 days night (22–06) followed by 7 d without working.	*Across-shift lung function changes* Morning shift No change in lung function in either group. Afternoon shift Significant decreases in spirometric indices in the exposed group only, but interactions between exposure and time were not significant, except for VC ($P = 0.03$). Night shift Significant decreases in spirometric indices in the exposed group, only. Interactions between exposure and time were significant for: FEV_1: 3.0% vs 1.1% ($P = 0.03$) FEV_1/VC: 2.3% vs 0.8% ($P = 0.002$) $FEF_{25–75}$: 7.7% vs 1.0% ($P = 0.02$).	Lung function tests at the beginning, in the middle, and at the end of the first (day 1) morning shift, the last (day 14) afternoon shift and the last (day 21) night shift.	(80)	Support for a combined effect of dust exposure and shift work [1]

Table 6. Studies on shift work and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Shift work	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
Cohort: 57 workers (mean age 36 y) exposed to fumes containing zinc oxide in a steel plant (production or maintenance) in Belgium. *Referents:* 55 non-exposed workers (mean age 38 y) (maintenance or strandcasting department).	*Personal sampling* Total dust (prior to the study): 1.0–22.8 (mean 8) mg/m^3 with an average of 39% in the respirable range (< 5 µm). Zinc oxide: below or close to the TLV for fumes (5 mg/m^3) at ground floor level, but exceeding that value in the upper floors (7.6 mg/m^3). Urinary zinc post-shift, mg/g creatinine: 0.33 vs 0.24 in exposed and referents (P = 0.002).	Most subjects worked 21 consecutive days (7 d/shift) followed by 7 d without working. Some subjects worked normal day shifts with 2 days off at the weekend.	*Across-shift lung function changes (spirometry)* Day shift Small decreases in VC and in FEV_1 in most workers. These decreases did not differ significantly between exposed and referents. Night shift VC and FEV_1 decreased significantly in exposed (-99 ± 178 ml and -140 ± 140 ml, respectively), but not in referents (-25 ± 159 ml and -51 ± 213 ml). No significant differences between exposed and referents. The decrease in FEV_1 was maintained the day after exposure. The cross-shift decrease in lung function was noticeable only across the night shift. The effects on lung function were small but likely represent a subclinical response to the inhalation of small quantities of zinc oxide.	Lung function test before and after shift on the 1st working day after rest, and on the 2nd day after the work shift. Lung function in referents was measured on one single shift, not necessarily being the first working day after rest.	(87)	Some support for a combined effect of zinc oxide exposure and night shift work [1]
Cohort: 97 male shift workers in the potato processing industry, the Netherlands.	*JEM* based on categorisation of job by plant with 27 categories. *Endotoxins* Estimated overall geometric mean exposure: 534 EU/m^3 (53–8 167 EU/m^3).	*Sequence of shift rotation*: afternoon → morning → night → afternoon, etc.	*Across-shift changes in lung function (PEF)* Work schedules Morning +2.7% Afternoon -1.3% Night -1.7% (consistent with expectations, based on the circadian rhythm). Endotoxins Change in PEF (%) associated with an increase	Smoking and atopy were not important confounding or effect-modifying factors in the observed relationships.	(120)	Indicates a combined effect of endotoxin exposure and night shift work [1]

Table 6. Studies on shift work and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Shift work	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
		A work period lasted 3–4 d, with a subsequent leisure period of 2–3 d.	in exposure from 249 to 1 411 EU/m^3 (interquartile range) Morning -0.46% ($P < 0.05$ vs afternoon) Afternoon -1.78% Night -0.83% ($P < 0.10$ vs afternoon) A higher endotoxin exposure was associated with an increased prevalence of work-related symptoms.			
Repeated measures design *Cohort*: 8 males from a cellulose acetate manufacturing plant, Germany. *Referents*: 8 male workers in the packing department. Mean age: 38 y.	*Personal sampling 2 × 4 h/day* Acetone: 980 ppm (mean).	Cohort + referents 3-shift work: Morning → afternoon → night starting at 06, 14 and 22.	*Quality of sleep* Acetone exposure Less sleep recovery ($P = 0.05$) Acetone exposure × night shift Low recovery ($P = 0.005$) Easy falling asleep ($P < 0.1$) Low depth of sleep ($P < 0.1$) Dose-response relationships were found between acetone in air and urine during the three different work shifts and sleep quality.	Quality of sleep was recorded after night-time or daytime sleep that followed exposure.	(68)	Some support for a combined effect of acetone exposure and night shift work. It cannot be determined whether indirect homeostatic and/or direct pharmacologic/ chronotoxicologic factors are responsible for this daytime time-dependent difference between exposed and referents [1]

Table 6. Studies on shift work and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Shift work	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
Cohort: 37 male production and maintenance workers in a fibreglass wool manufacturing plant, US.	*Personal sampling 2 × 4 h/day, 8-h TWA*s Person-days were stratified: Endotoxins, ng/m^3 0.4–4.3 (low) 4.3–15.4 (medium) 15.7–759 (high) Formaldehyde 1.2–265 µg/m^3 Phenolic resin 5.7–327 µg/m^3, levels were frequently < DL.	*Production workers:* Rotated between 1st shift (06–14) and 3rd shift (22–06) *Maintenance workers:* Only day shifts (07–15).	Lung function changes (≥ 5% decline in PEF) *Endotoxins* Across work shift (OR, 95% CI) Medium 5.5 (1.0–30) High 6.8 (1.0–46) Start of shift to arising the next morning (OR, 95% CI) Medium 2.4 (1.0–5.6) High 2.5 (1.1–5.9) *Phenolic resin and formaldehyde* No decrements in PEF. *Work schedule* Evident effect of normal diurnal variation in PEF seen as a much higher frequency of 5% across-shift declines at night than during the morning shift, independent of chemical exposure.	PEF was measured by spirometry on the same days as the exposure measure-ments. Pre- and post-shift PEF were obtained on at least 2 days. PEF was obtained for totally 181 days off work and 187 days at work. All analyses controlled for shift (dichotomous).	(76)	Insufficient support for a combined effect of exposure to endotoxins, formaldehyde or phenolic resins and night shift work [2]
Other outcomes						
Repeated measures design *Cohort A:* 8 male cleaners working in floor covering production, Germany. *Referents*: 8 male workers in the packing department in the same firm.	*Cohort A* 15 solvents from printing colours and cleaning agents were quantified in 110 personal full-shift air samples/dosimeters. 12 of the solvents were clearly below 25% of the German	*Rotating shift work*: Cohort A + referents 2-shift work starting at 05 and 13. Cohort B + referents 3-shift work:	Neurobehavioral effects studied: a) Performance (reaction time, colour word vigilance) b) Acute symptoms (discomfort, irritations, breathing difficulties) c) Well-being (tension, tiredness, complaints and annoyance). *Cohort A (mixed solvents + 2-shift)* Mixed solvents No effects.	Measurements were taken at 3 time-points during 3 complete mornings, afternoon, night shift cycles of 3 weeks following each other.	(67)	Some support for a combined effect of exposure to mixed solvents or acetone and shift work [1]

Table 6. Studies on shift work and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Shift work	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
Mean age: 44 y. *Cohort B*: 8 males from a cellulose acetate manufacturing plant, Germany. *Referents*: 8 male workers in the packing department. Mean age: 38 y.	MAK-value. Concentrations of 1-methoxy-propanol-2, cyclohexanone, 2-butoxyetanol exceeded 25% of MAK. *Cohort B* *Personal sampling 2 × 4 h/day* Acetone: 980 ppm (mean) (68).	Morning → afternoon → night starting at 06, 14 and 22.	Shift Tiredness and annoyance: $P < 0.05$ Mixed solvents/shift Tension and tiredness: $P < 0.05$ Mixed solvents/across shift Reaction time and annoyance: $P < 0.05$ Shift/across shift Reaction time, tension and tiredness: $P < 0.05$ Mixed solvents/shift/across shift No association *Cohort B (acetone + 3-shift)* Acetone Acute symptoms: $P < 0.05$ Well-being: $P < 0.05$ (for each) Shift Performance: $P < 0.05$ (for each) Acute symptoms: $P < 0.05$ Acetone/shift No effects. Acetone/across shift Acute symptoms: $P < 0.05$ Well-being: $P < 0.05$ (for each) Shift/across shift Colour word vigilance: $P < 0.05$ Acute symptoms: $P < 0.05$ Tension and tiredness: $P < 0.05$ Trends for tiredness and colour word vigilance within shift, differed more from referents during			

Table 6. Studies on shift work and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Shift work	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
			the morning shift than during the other shifts, although the exposed group revealed the highest values of tiredness during the night shift. Acetone/shift/across shift Colour word vigilance: $P < 0.05$. Overall Both exposure to acetone and shift work contributed to the strong adverse effects.			
Population-based case-control study *Cases*: 265 patients (90% women, mean age 39 y) with systemic lupus erythematosus (SLE), Carolina, US. *Controls:* 355 subjects identified through driver's license records, and frequency matched to patients by age, sex and state.	*In-persons interviews* Questions on job title, main tasks, type of company, duration of employment, job tasks with potential exposure to different solvents: questions on use of material: (age when use started, days/year, and number of years worked).	*In-person interviews* on working hours for each job held for ≥ 1 y (mostly days, mostly evenings, mostly nights, or rotating shifts). For analyses of shift work, night shifts or rotating shifts that included nights considered "positive".	*SLE (OR, 95% CI)* Chemical exposure Solvents: No associations Mercury: 3.6 (1.3–10.0), 10 cases Dental workers: 7.1 (2.2–23.4), 11 cases Shift work All: 1.6 (0.99–2.7) African-Americans: 2.3 (1.1–4.9) White workers: 0.82 (0.34–2.0) Logistic regression analyses. The influence of shift work and healthcare work were examined, adjusting for each of these factors, however the results did not differ substantially from the results for each of these exposures.	Adjustment for age, state, race and education.	(30)	No support for a combined effect of solvent exposure and shift work [2]

Table 6. Studies on shift work and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Shift work	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
Cross-sectional study *Cohort:* 968 women (18–54 y, mean 30.5 y) with ≥ 1 y work experience as direct production operators, in 18 semiconductor factories (15 semi-conductor assembly factories and 3 wafer fabrication factories) in Malaysia. Data collection: 1999–2000.	*Self-administered questionnaire* on exposure to chemical hazards: 1) whether chemicals were used by the workers (42% yes); and 2) whether there was any smell of any chemicals or dust while working (32% yes). Chemicals used included hydro-chloric and hydro-fluoric acids, hydro-gen peroxide, ammonia, epoxy resin, mould compound, various acids and alcohols, isopropyl alcohol and acetone.	*Self-administered questionnaire* Distribution of work schedules: Rotating 8-h shift: 61% (6 d/wk) Rotating 12-h shift: 30% (4 d work, 3 d rest, 3 d work and 4 d rest) Day shifts only: 9.3% (6 d/wk).	*Sick leave ≥ 1 d within the past year* Chemical exposure (OR, 95% CI) Smell chemicals 1.64 (1.01–2.67) Work schedule Significant association with workers on the 12-h rotating shift having the lowest proportion of sick leave ($P < 0.05$). Logistic regression.	Adjustment for marital status, work section, work schedule, use chemicals in work process, smell chemicals, and poor ventilation.	(27)	Insufficient information for evaluating a potential combined effect of chemical exposure and shift work [2]

Table 6. Studies on shift work and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Shift work	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
Cohort: 119 male workers (median age 32.0 y) employed ≥ 1 y with exposure to carbon disulphide (CS_2) in a viscose rayon factory in Belgium. *Referents*: 79 male workers (median age 34.3 y) without appreciable exposure to toxic substances, employed ≥ 1 y in a metal work, a plastic processing plant and a starch processing factory.	*Personal monitoring* in 17 jobs showed CS_2 exposures of 4–112 mg/m^3. Individual cumulative CS_2 exposure indexes were calculated, categorised as low or high. Working conditions had not changed since 1932.	*Self-administered questionnaire* included a multiple choice section on the type of work schedule (normal hours, shift work, etc.). 64.7% reported rotating shifts vs 84.8% among referents.	*Gastrointestinal complaints during last 3 mo, %, (self-administered questionnaire) + liver function* CS_2 exposure Anorexia, nausea, vomiting, flatulence ($P < 0.05$ for each). Liver size, liver enzymes ($P < 0.05$ for each). Shift work No significant association with any of the digestive complaints. Multiple logistic regression analysis.	For liver function tests, adjustment for alcohol intake, BMI and intake of medication. For gastrointestinal complaints, adjust-ment also for smoking, coffee consumption, commuting time, stress at work, shift work, educational level, family history of ulcer disease.	(111)	Insufficient information for evaluation of a combined effect of CS_2 exposure and shift work [2]

[a] Relevance category 1: Shift work defined according to the definitions in this report. Measures of chemical exposure may be quantitative or qualitative (exposed vs unexposed). The outcome is measurable as biomarkers or health effects. The studies include statistical analyses of the combined exposure to shift work and chemical exposure with respect to the outcome. When shift work is included as a factor in the analyses, a risk estimate for shift work should be presented, including confidence interval/P-value.
Relevance category 2: The same definition of shift work and measures of chemical exposure and of outcome as for relevance category 1. However, no risk estimates are presented from statistical analyses of the effect of shift work.
BMI: body mass index, CI: confidence interval, DL: detection limit, ECG: electrocardiogram, EU: endotoxin unit, $FEF_{25–75}$: forced expiratory flow between 25% and 75% of VC, FEV_1: forced expiratory volume in 1 second, HDL: high density lipoprotein, HI: hazard index, JEM: job exposure matrix, LDL: low density lipoprotein, MAK: Maximale Arbeitsplatz-konzentration (maximum workplace concentration), OR: odds ratio, PEF: peak expiratory flow, RR: relative risk, SGA: small for gestational age, SLE: systemic lupus erythematosus, SMR: standardised mortality ratio, SRR: standardised rate ratio, TLV: threshold limit value, TWA: time-weighted average, US: United States, VC: vital capacity.

Table 7. Studies of extended working hours and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Working hours	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
Reproductive effects						
Cross-sectional study *Cohort:* 907 pregnant working women receiving prenatal care at two hospitals in Thailand. Retrospective data collection conducted March–November in 1995.	*Personal interviews* Exposure to paints, varnish, lacquer, dyes, pigments, inks, solvents, welding fumes, insecticides, herbicides, wood preservative agents, anaesthetic gas, X-ray films or radioactive agents. *Exposure groups* 1: 2–3 times/wk or most of time. 0: occasionally or never (dominating choice).	*Personal interviews* Working h/wk ≤ 40 41–50 51–60 61–70 ≥ 71.	Time to pregnancy *Long working hours (> 71 h/wk vs ≤ 60 h/wk)* Women (> 9.5 mo) First pregnancies 2.3 (1.0–5.1) All pregnancies 1.6 (1.0–2.7) Women and men First pregnancies 4.1 (1.3–13.5) All pregnancies 2.0 (1.1–3.8) *Potentially reprotoxic chemicals* No association. Logistic regression.	Adjustment for age, education, BMI, menstrual regularity, obstetric and medical history, coital frequency, and potential exposure to reproductive toxic agents (yes/no), but the impacts of the respective con-founders were not analysed.	(108)	Insufficient information for evaluation of a combined effect of chemical exposure and extended working hours [2]
Biomarkers of disease						
Cohort: 13 workers of which 6 with 8-h shift (mean age 40.0 y) and 7 with 12-h shift (mean age 28.9 y), exposed to carbon disulphide (CS_2) in the spinning department in the viscose rayon industry, Taiwan.	*Average CS_2 exposure (personal), 5 consecutive days* Air levels (TWA) and urinary TTCA collected pre- and post-shift.	8-h or 12-h work shifts.	*Carbon disulphide in air (ppm)* 12-h shift: 11.3 ± 1.47 8-h shift: 6.3 ± 0.64 P < 0.001 *TTCA in urine (mg/g creatinine)* Pre-shift 12-h shift: 1.78 ± 1.04 8-h shift: 0.76 ± 0.63 P < 0.001 Post-shift 12-h shift: 5.88 ± 2.04	Data collection included personal interview including basic demographic data, duration of employment, medication and disease history, and data from an annual health examination report, including	(100)	No support for a combined effect of CS_2 exposure and extended working hours [1]

Table 7. Studies of extended working hours and implication on risk assessment (health) of chemicals.

Study design	Chemical exposure	Working hours	Results	Remarks	Ref.	NEG conclusion [Relevance category 1 or 2] [a]
			8-h shift: 3.24 ± 1.21 P < 0.001 *Ratio (pre-shift urinary TTCA)/(airborne CS_2 levels on the preceding day)* Significant linear accumulation trend across the workdays for the 12-h shift (r = 0.98, P = 0.02).	renal function status.		
Cohort: 53 workers (40 males , 13 females) employed > 5 y at a lead storage battery factory in Japan followed for 7 y.	*Lead in air* Monitored once a year at 31–42 sites (area sampling). Geometric means 0.041–0.118 mg/m^3, depending on the year of the survey. *Lead in blood* Determined once a year for the last 4 y. *ALA in urine* Measured twice a year for 7 y.	*Questionnaire survey* ≥ 8.5 h/day 1979: 28% 1980: 44%.	Lead in blood, but not in air, correlated with ALA in urine. The semi-annual production rate of batteries correlated with changes in mean ALA in urine (7 y). Changes in ALA between 1979 and 1980 Mean ALA in urine increased by 1.4 mg/l. Incidence of higher-than-normal urinary ALA increased.	No smoking permitted in the factory during working hours. Age not included in the analysis.	(97)	Insufficient information for evaluation of a combined effect of lead exposure and extended working hours [2]

[a] Relevance category 1: Extended working hours defined as > 8 hours/day or > 40 hours/week. Measures of chemical exposure may be quantitative or qualitative (exposed vs unexposed). The outcome is measurable as biomarkers or health effects. The studies include statistical analyses of the combined exposure to extended working hours and chemical exposure with respect to the outcome. When extended working hours is included as a factor in the analyses, a risk estimate for extended working hours should be presented, including confidence interval/P-value.

Relevance category 2: The same definition of extended working hours and measures of chemical exposure and of outcome as for relevance category 1. However, no risk estimates are presented from statistical analyses of the effect of extended working hours.

ALA: δ-aminolevulinic acid, BMI: body mass index, TTCA: 2-thiothiazolidine-4-carboxylic acid, TWA: time-weighted average.

7. Existing approaches for adjustment of OELs for unusual working hours

7.1 Shift work

To our knowledge, models for adjusting OELs for specific work shifts associated with potential effects on circadian rhythms such as night work, have not been published.

7.2 Extended working hours

In toxicological terms, for many chemicals, an equilibrium is established between the accumulation of a contaminant in the body during the time at work and the elimination of the contaminant during the time away from work (this period is assumed to be exposure-free) until the maximum body burden or accumulation plateau in the body is reached. Day-to-day increases in toxicant concentration at the site of action might occur to a greater degree during extended work shifts than during standard 8 hour/day schedules. The goal of adjusting OELs in air is to identify an exposure level that ensures that the daily or weekly peak body burdens, and the associated health risks, are not exceeded during extended working hours compared to a normal 8 hours/day, 5 days/week shift.

Many models have been used to adjust OELs for extended work schedules in order to compensate for the greater exposure during the extended work shift and the decreased recovery time between shifts.

The most accurate and scientifically credible adjustment of 8-hour time-weighted average (TWA) OELs to extended working hours, are based on pharmacokinetic models (4). It requires an understanding of the toxicokinetics of the substance, its toxicological effects, the underlying mechanism for those effects and the basis on which the OEL was derived. For many substances, the required toxicokinetic information may not be available, and also due to the potential complexity of these models, this approach is not readily applicable to many substances. Simpler approaches have been developed, and will be discussed below.

Before any adjustment of an exposure standard is attempted, the basis of that OEL must be understood, so as to determine whether it is appropriate to adjust for non-traditional work shifts, and if so, which model to apply. It is not necessary to adjust short-term exposure limits (STELs) (normally the 15-min TWA), and ceiling limits (the concentration that should not be exceeded during any part of the working exposure), as these are associated with acute rather than chronic exposures.

Figure 6 illustrates blood concentrations during two work weeks of exposure to chemicals with different biological half-times. For a chemical with a half-time of less than 3 hours accumulation will not occur since virtually all of the chemical is excreted prior to the next exposure. A chemical with a half-time of 1 day (24 hours) will have a slight accumulation during the work week with no additional increase the following weeks. In contrast, a half-time of 1 month leads to accumulation over several months.

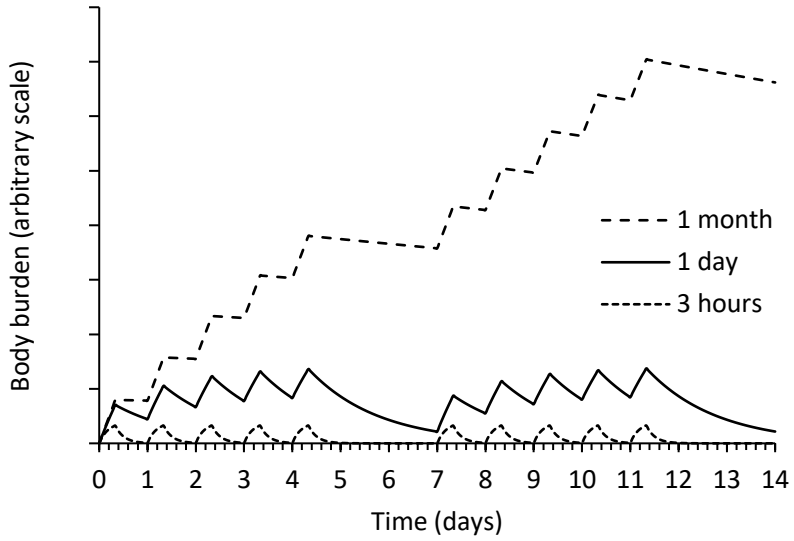

Figure 6. Body burden over two work weeks (2 × 5 days, 8 hours/day) with constant exposure to chemicals with different biological half-times.

For chemicals with longer biological half-times than 3 hours, accumulation may also occur during normal 8 hour/day shifts since another exposure starts before all of the chemical from the previous exposure is eliminated (Figure 6). The peak blood level increases with each dose until it reaches a maximum, or steady-state, when the rate of elimination equals the rate of absorption. Once at steady-state, the peak blood level will remain at this level, even though exposure is maintained every 24 hours. For example, for organic solvents with half-times in the range 12–60 hours, the steady-state body burden will be reached after approximately 2–6 weeks of repeated exposures. For shorter half-times steady-state will be reached after about 2–4 workdays. A rule of thumb is that steady-state body burdens occur after an exposure period greater than five biologic half-times. However, accumulation of a chemical during an exposure period (week or year) is not necessarily detrimental as long as the peak or steady-state tissue level do not reach levels that are above the threshold concentration for adverse health effects.

A potential problem related to unusual working hours is illustrated in Figure 7, which indicates that the peak body burden of a chemical with a biological half-time of 24 hours might differ with different shift schedules even when the total weekly dose (40 hours × 50 ppm) is the same. In such cases, the air concentration of the chemical has to be reduced, to ensure that the peak tissue concentration for the unusual exposure schedule does not exceed the presumable “safe” level of the normal schedule.

The models described above consider the body as a single compartment, with one biological half-time for a chemical. However, many chemicals have several half-times corresponding to the respective elimination rates from different organs or the internal dose at different target organs for a given level, duration and pattern of exposure to a chemical.

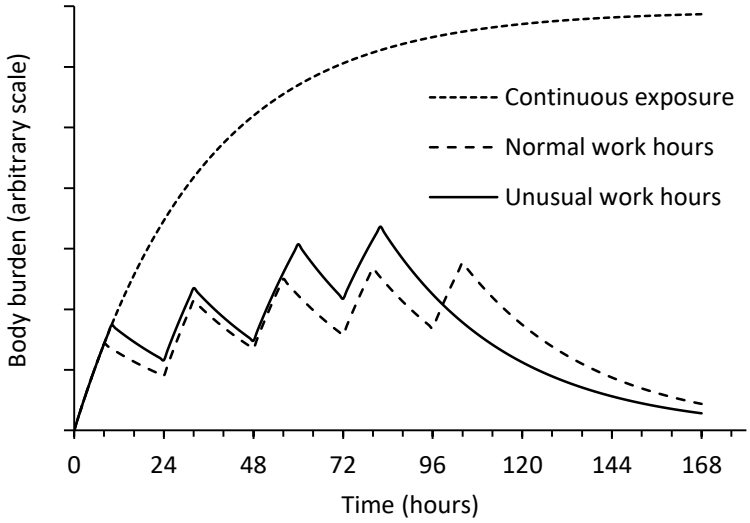

Figure 7. Accumulation of a chemical over a work week could vary with different shift schedules, even though the total weekly dose is the same. In this example, the normal working hours are 8+8+8+8+8 = 40 and the unusual working hours are 10+8+12+10 = 40. The exposure is assumed to remain constant during work and the biological half-time is 24 hours. Adapted from Paustenbach 2011 (89).

7.3 Implications for biological limit values

A biological limit value (BLV) refers to a maximum permissible concentration or excretion rate of an exposure biomarker. The biomarker is typically the chemical itself or its metabolite in blood, urine or exhaled air. As the biomarker reflects the internal dose the BLV should, in principle, not be adjusted for longer work hours. However, there are several exceptions to this rule, for example if the chemical has a long half-time in the target organ compared to the elimination half-time of the biomarker. One example is poorly soluble substances that accumulate and exert their effects in the lungs.

7.4 Existing methods for adjustment of OELs by time extrapolation tools

7.4.1 Brief and Scala model

The Brief and Scala method considers both the increased uptake due to increased hours worked and the reduced recovery time between exposure periods (22).

Adjustment factors for daily and weekly exposures are addressed by the following formulae:

1) Daily adjustments of 8-hour OELs:

Daily adjustment factor = $\{8/h_d \times (24 - h_d)/16\}$, where;

8 = hours worked on a normal day

h_d = hours worked per day

$24 - h_d$ = exposure free time (recovery time) between exposure periods

16 = exposure free hours for an 8-hour workday.

Adjusted OEL = OEL × daily adjustment factor

Example: A worker is exposed to toluene for a 12-hour shift. The 8-hour OEL for toluene is 50 ppm. Using the Brief and Scala model the adjusted OEL is calculated the following way:
Daily adjustment factor = $\{8/h_d \times (24 - h_d)/16\} = \{8/12 \times (24 - 12)/16\} = 0.5$
Adjusted OEL = OEL × daily adjustment factor = 50 ppm × 0.5 = 25 ppm

2) Weekly adjustment of 8-hour OELs:

For a 7-day work week, the Brief and Scala model is based upon a 40-hour work week.

Weekly adjustment factor = $\{40/h_{wk} \times (168 - h_{wk})/128\}$, where;

40 = hours worked in a normal work week
h_{wk} = hours worked per week
168 = hours per week (24 h × 7)
168 - h_{wk} = exposure free hours per week
128 = exposure free hours for a 40-h work week (16 h × 5 + 24 h × 2).

Adjusted OEL = OEL × weekly adjustment factor

The adjusted exposure limit should be calculated using each equation (daily and weekly adjustment) and the most restrictive value adopted. Arguments in favour of the Brief and Scala model are that it:

- is simple to use,
- takes into account both increased hours of exposure and decreased exposure free time, and
- is more conservative than other models.

7.4.2 Haber's rule (direct proportion model)

Another approach is to adjust OELs in direct proportion to the hours worked. Haber's rule from the early 1900s states that, for a given poisonous gas, there is a relationship between the concentration of exposure (C) and the duration of exposure (t) leading to the same biological response, i.e., C × t = k, where k is a constant, depending on both the gas and the effect. Thus, for instance the rule states that doubling the concentration will halve the time to achieve the same toxic effect.

For example, for a 10-hour shift:

Adjusted OEL = OEL × 8/(hours worked) = OEL × 8/10

Applying Haber's rule to the example of 12 hours exposure to toluene in the previous section gives the following:

Adjusted OEL = 50 × 8/12 = 33 ppm

As evident from this example, the Brief and Scala model is more conservative than Haber's rule.

When applying Haber's rule to adjust OELs for extended working hours there are several limitations. The information reported by Haber is based on the acute exposure to a small number of poisonous gases (including phosgene, hydrogen cyanide, chloroacetone and chlorine) and the time before death in cats (LC_{50}, lethal concentration for 50% of the animals at single inhalation exposure). Haber's rule has been widely used for time concentration extrapolations although it is known that outside a specific range or for other chemicals and conditions, in many instances it may not hold (75). The cumulative exposure constant may not relate to all responses or physiologic endpoints that may occur at lower exposure concentrations. This is of particular concern when different mechanisms exist for different toxic endpoints (23). For instance, following chlorine inhalation in mice different non-lethal endpoints indicative of lung injury were differentially affected by the different combinations of exposure concentration and time although the cumulative exposure dose was constant (54). For compounds causing sensory irritation at relatively low concentrations, such as ammonia, chlorine and formaldehyde, varying exposure concentration had a proportionally greater effect on sensory irritation than did changing exposure duration, probably due to adaptation (101). However, substantial quantitative data derived from studies on different toxic endpoints are lacking for most compounds. Another shortcoming is evident at low exposure concentrations when using Haber's rule for compounds with a high rate of detoxification/elimination. For such compounds, like hydrogen cyanide, the short biological half-times can negate effects from extended exposures (75).

Thus, although based on experimental studies Haber's rule has been validated only for a small number of toxic compounds at lethal concentrations, and may not relate to other adverse health endpoints exhibiting other mechanism of toxicity at lower exposure concentrations.

7.4.3 Modified Haber's rule

An assessment by ten Berge *et al.* of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical-specific, and even a toxic endpoint-specific exponent, C represents the airborne concentration while t represents the exposure duration (107).

ten Berge *et al.* examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death (LC_{50}), for approximately 20 structurally diverse irritative or systemically acting vapours and gases from a review of 20 studies of rats, mice, guinea pigs, cats, dogs, rabbits, monkeys and goats. He found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals (Table 8). Haber's rule is the special case where n = 1. ten Berge *et al.* concluded that the concentration-time relationship (i.e. value for n) should be determined empirically from acute inhalation exposure toxicity data on a chemical-specific basis (107).

Table 8. Estimates of the exponent (n) fitted to the equation ($C^n \times t = k$), where C is the LC_{50} value and t is the exposure duration. The 95% confidence intervals (CIs) reflect the variability in the data from 20 inhalation studies with rats, mice, guinea pigs, cats, dogs, rabbits, monkeys and goats (107). The influence of n on the shape of the equation is illustrated in Figure 8.

Gas or vapour	n	95% CI	Gas or vapour	n	95% CI
Local irritants			*Systemic action*		
Ammonia (NH_3)	2.0	(1.6–2.4)	Hydrogen cyanide (HCN)	2.7	(1.8–3.7)
Hydrogen chloride (HCl)	1.0	(0.7–1.3)	Hydrogen sulphide (H_2S)	2.2	(1.6–2.7)
Chlorine pentafluoride (ClF_5)	2.0	(1.4–2.6)	Methyl *t*-butyl ether ($C_5H_{12}O$)	2.0	(1.0–2.9)
Nitrogen dioxide (NO_2)	3.5	(2.7–4.3)	Methylenechlorobromide (CH_2ClBr)	1.6	(1.4–1.8)
Chlorine (Cl_2)	3.5	(2.5–4.4)	Ethylenedibromide ($C_2H_4Br_2$)	1.2	(1.1–1.2)
Perfluoroisobutylene (C_4F_8)	1.2	(1.1–1.4)	Tetrachloroethylene (C_2C1_4)	2.0	(1.4–2.6)
Crotonaldehyde (C_4H_6O)	1.2	(1.1–1.3)	Trichloroethylene (C_2HCl_3)	0.8	(0.3–1.4)
Hydrogen fluoride (HF)	2.0	(1.2–2.8)	Carbon tetrachloride (CCl_4)	2.8	(1.9–3.7)
Ethylene imine (C_2H_5N)	1.1	(0.8–1.3)	Acrylonitrile (C_3H_3N)	1.1	(1.0–1.2)
Bromine (Br_2)	2.2	(2.0–2.4)			
Dibutylhexamethylene-diamine ($C_{14}H_{32}N_2$)	1.0	(0.6–1.4)			

LC_{50}: lethal concentration for 50% of the animals at single inhalation exposure.

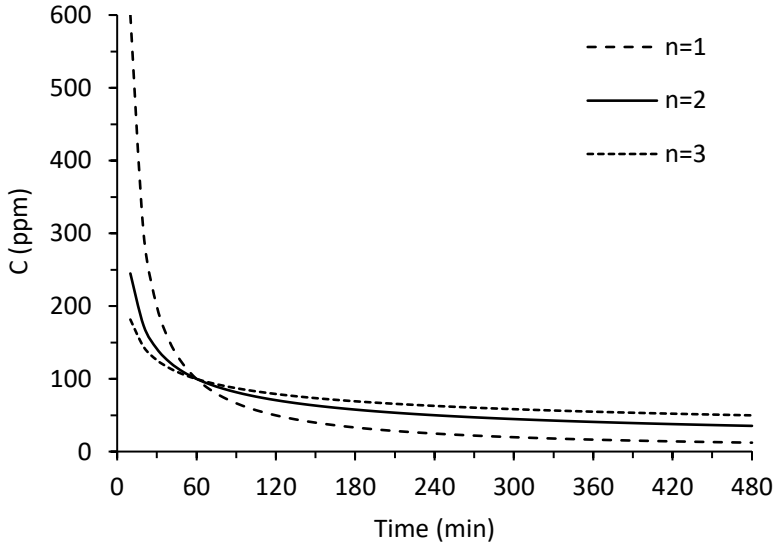

Figure 8. Effects of varying n in the equation $C^n \times t = k$ (modified Haber's rule). For ease of comparison, the concentration (C) is set to the same value (100 ppm) for all three curves. Adapted from the National Research Council 2001 (81).

Figure 8 indicates that when extrapolating from 60 min to longer exposure durations, i.e., up to 8 hours, the lower the value of n, the lower the extrapolated value. Thus, n = 1 yields a more conservative value, i.e. a lower adjusted exposure limit, than any value of n > 1. When extrapolating from 60 min to shorter exposure durations, the higher the value of n, the lower the extrapolated value. Therefore, a value of n = 3 yields a more conservative value than any value of n < 3.

An approach to generate toxicity values for time scaling is taken by the NAC/AEGL Committee to derive Acute Exposure Guideline Levels (AEGLs) from empirical data (81).

1) If appropriate toxicological data for the exposure concentration-exposure duration relationship of a specific health-effect endpoint are available for the AEGL-specified exposure periods, use the empirical data directly.
2) If empirical exposure concentration-exposure duration relationship data are available, but do not comply with the AEGL-specified exposure periods, use the available data to derive values of n and extrapolate using the equation $C^n \times t = k$. If supporting data are inconsistent with the extrapolated AEGL value, the value of n might be modified.
3) If no empirical exposure concentration-exposure duration relationship data are available, a value of n = 1 for extrapolating from shorter to longer exposure durations, and a value of n = 3 for extrapolating from longer to shorter exposure durations should be tested initially. The final value(s) of n may be modified based on supporting data.
4) If there are no supporting data, a default value of n = 1 for extrapolating from shorter to longer exposure periods and a default value of n = 3 for extrapolating from longer to shorter exposure periods should be selected as these values lead to the most conservative estimates.

The ten Berge modification of Haber's rule extrapolates for exposures up to 8 hours, but its applicability for longer exposure durations was not discussed in the original paper. As evident from Figure 8, the $C^n \times t$ curves could be extrapolated with minimal error when the time points are located on the part of the curve asymptotically approaching the axes of the coordinates, i.e., when extrapolating beyond 8 hours. However, as the exposure time increases the biological half-time of the toxic compound should be taken into account (45). Internal exposure (in blood) of agents with a short half-time will level off even during a conventional 8-hour shift and remain unchanged if the shift is extended, even though its cumulative internal exposure increases. On the other hand, the internal levels and cumulative exposure of agents with a long half-time slowly rise when the exposure is extended. These considerations also have implications on the association between extended working hours and different classes of adverse effects. Some effects, such as diminished vigilance, analgesia, and irritation, are related to the biological levels at the target site and thus to the highest concentration of the agent in the blood. Other toxic endpoints, such as carcinogenicity and hepatotoxicity, are related to the cumulative exposure.

The limitations discussed for Haber's rule also apply to the ten Berge modification. It is recognised that the time-scaling relationship observed with a lethality endpoint based on LC_{50} may not accurately describe irreversible, non-lethal or reversible endpoints. However, this approach is believed to be scientifically credible if the mechanism of toxicity for lethal and non-lethal irreversible effects is thought to be similar. The Standing Operating Procedures (SOPs) of the National Research Council (NRC) (81) suggest that if data indicate different toxicological mechanisms for lethal effects and non-lethal irreversible health effects, the lower bounds of n = 1 should be used for extrapolation from shorter to longer exposure periods. The resultant AEGL values should then be evaluated using all supporting data and adjusted accordingly.

7.4.4 Quebec model

The Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST) in Quebec, Canada, has published a guide for the adjustment of OELs for extended work schedules, the so-called Quebec model (55). The model is based on Haber's rule and assumes that the intensity of a toxic response is a function of the concentration that reaches the site of action. Depending on the type of toxic effect, an appropriate adjustment factor (including no adjustment, i.e. a factor 1) is selected and applied to the substance's OEL (Table 9). This model is intended to ensure that for substances with acute or chronic toxicity, the daily dose, or the weekly dose respectively, during an altered work shift does not exceed the dose obtained in a conventional 8-hour work shift. For substances that produce effects following short-term exposure (Category II substances in Table 9), the daily adjustments are 8 (hours) divided by the average exposure duration in hours per day. Thus, if a person is exposed for 12 hours the adjustment factor would be 0.67. No adjustments are made for exposures and toxic effects that are unrelated to the body burden. No adjustment is applied for simple asphyxiants, for substances regulated by a ceiling value, for irritants and for malodourous substances (Category I, Table 9). No adjustment is made for STELs.

Table 9. IRSST adjustment categories (55).

Category	Adjustment classification	Type of adjustment
I-a	Substances regulated by a ceiling value.	None
I-b	Irritating or malodorous substances.	None
I-c	Simple asphyxiants, substances presenting a safety risk[a] or a very low health risk[a], whose half-time is less than 4 hours. Technological limitations.	None
II	Substances that produce effects following *short-term* exposure.	Daily
III	Substances that produce effects following *long-term* exposure.	Weekly
IV	Substances that produce effects following a *short-* or *long-term* exposure.	Daily or weekly, the most conservative of the two

[a] Explanation missing.

IRSST: Institut de recherche Robert-Sauvé en santé et en sécurité du travail.

Each chemical is assigned in one of six categories based on the toxic effect (Table 9). Depending on the category assigned, a recommendation will be made with either:

- no adjustment to the exposure standard,
- a daily or weekly adjustment, or
- the most conservative of the daily or weekly adjustments where both apply.

In assigning a chemical to a particular adjustment category, toxicological information was reviewed including sensitisation, irritation, organ toxicity, reproductive system toxicity and teratogenicity (113). The report includes a list where they defined the adjustment category for each of the 705 substances listed in the Regulation respecting Occupational Health and Safety (ROHS). The categories are also available online by chemical name and by CAS number (56).

Substances that produce effects following short-term exposure have OELs that prevent excessive body accumulation during 8 hours of exposure (e.g. carbon monoxide). Substances that produce effects following long-term exposure present cumulative hazards, and have OELs that prevent body accumulation over days or even many years of exposure (e.g. lead and mercury).

The daily and weekly adjustments are the average exposure duration in hours per day or hours per week, respectively and based on a repetitive work cycle;

Adjustment factors:

$8/h_d$ *Category II* substances, requiring a *daily* adjustment

$40/h_{wk}$ *Category III* substances, requiring a *weekly* adjustment

h_d = exposure duration in hours per shift

h_{wk} = average duration of work shifts in hours per week *based on a repetitive work cycle*.

In no case can the adjusted OEL be greater than the OEL, thus the model does not allow adjustment factors > 1 for workdays < 8 hours.

More information on this model and how to perform the adjustment, is provided in the document “Guide for the Adjustment of Permissible Exposure Values (PEVs) for Unusual Work Schedules” (55).

7.4.5 Pharmacokinetic models

Pharmacokinetic models use information such as the biological half-time of the substance and exposure time to predict peak body burden for a given work schedule. These models aim to ensure that the maximum body burden for the “unusual” work routine does not exceed that for a normal work shift. The pharmacokinetic models are generally considered more accurate than other models, but can involve complicated calculations and biological half-times of substances which are not always available. The Brief and Scala model is generally more conservative than the pharmacokinetic and Quebec models (Figure 10).

However, the pharmacokinetic models are suitable only for chemicals with standards based on accumulated body burden, while they are not suitable for

chemicals with standards based on odour, irritancy or other non-systemic health effects.

There are several different pharmacokinetic models available. The one most widely used is the one-compartment Hickey and Reist model (53) which requires knowledge of the substance's biological half-time, the hours worked per day and hours worked per week:

$$Fp = \frac{(1 - e^{-kt_{1n}})(1 - e^{-k(t_{1n}+t_{2n})n})(1 - e^{-kT_s})(1 - e^{-k(t_{1s}+t_{2s})})}{(1 - e^{-kt_{1s}})(1 - e^{-k(t_{1s}+t_{2s})m})(1 - e^{-kT_n})(1 - e^{-k(t_{1n}+t_{2n})})}$$

Where:

Fp = pharmacokinetic adjustment factor

k = biologic elimination rate = (ln 2)/$T_{1/2}$, where $T_{1/2}$ = the biological half-time

t_{1n} = length of the standard workday (8 hours)

t_{2n} = length of the standard recovery period (16 hours)

$t_{1n} + t_{2n}$ = the length of the day (24 hours)

T_n = length of the week (7 days or 168 hours)

m = number of workdays per week in the special schedule

n = number of days in standard work week (= 5)

t_{1s} = length of the extended shift workday (in hours)

t_{2s} = length of the rest period between extended shift workdays (in hours)

$t_{1s} + t_{2s}$ = length of the extended shift "day" (usually, but not always 24 hours)

T_s = total length of the periodic work cycle (number of days worked and days in the rest period [in hours])

Several follow-up papers using the same formula and applying it to adjust the OEL for various substances have been published [see e.g. refs (11, 33, 74, 113)]. In addition, a number of graphs have been published that demonstrate the application of the formula to a range of exposure schedules (Figure 9).

Generally, the one-compartment model predicts that no adjustment of OELs is necessary for substances with very long (over 1 000 hours) or very short (less than 1 hour) half-times, but that adjustments are necessary for substances with intermediate half-times (usually 6–100 hours). For an agent with a long half-time (e.g. mineral dust), the adjustment factor is approximately proportional to the ratio of the number of hours exposed in the work cycle compared to a normal 40-hour week (89). Paustenbach (89) suggested some rule of thumbs related to Figure 9. Adjustments of OELs are not generally necessary for extended work shifts if the biological half-time of the toxicant is less than 4 hours or greater than 400 hours. Furthermore, whenever the biological half-time is unknown, a "safe" level can be estimated by assuming that the chemical has a biological half-time of about 20 hours. This will generally yield the most conservative adjustment factor for typical 8-, 10-, 12- and 14-hour workdays.

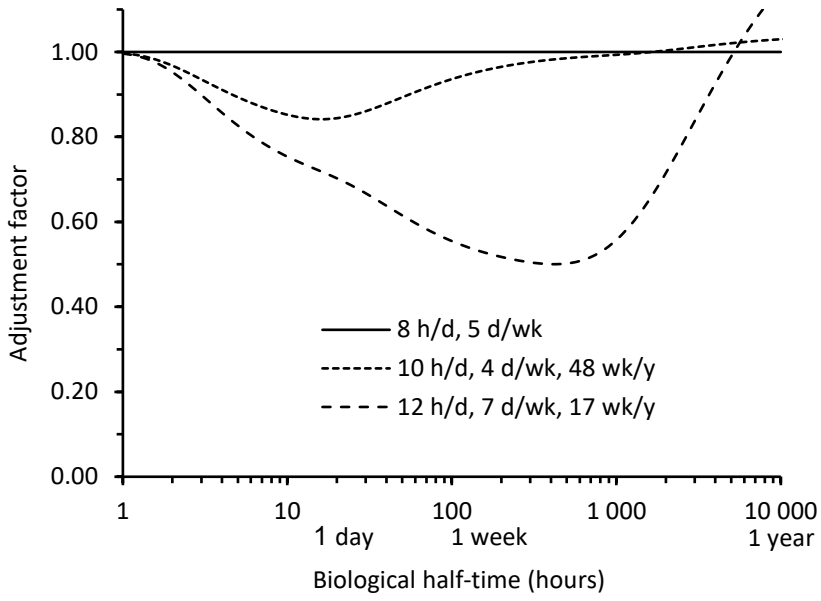

Figure 9. Adjustment factor for three work schedules as a function of the biological half-time of the chemical. The curves were calculated according to Hickey and Reist (53). The lower curve corresponds to a common arrangement in the offshore industry of 12 hours of work per day for 2 weeks, followed by 4 weeks off.

To address the adjustment for substances with unknown half-time more exactly, Armstrong *et al.* developed a calculator in MS Excel. In this calculator, only the extended shift information is entered (hours/day, days/week). The lowest adjustment factor and the corresponding half-time are then back-calculated using the Solver function (11).

7.4.6 Physiologically based toxicokinetic (PBTK) model

Several physiologically based toxicokinetic (PBTK) models have been used the last decades to estimate the internal dose at target organs from environmental exposures [see e.g. Johanson for description and examples of different applications (64)]. PBTK models have also been applied to adjust OELs for unusual working hours (5, 11, 74). In these models, the body is divided into anatomical compartments representing individual organs or tissue groups. The transport of chemical in the body is described by mass balance equations that incorporate blood flows, partitioning into compartments and tissue volumes. After incorporation of elimination processes like metabolism and excretion, the internal dose of the chemical (and/or its metabolites) at the target organ can be estimated. Also the impact of workload, which determines cardiac output and alveolar ventilation rates, and dermal uptake could be introduced in these models. Notably, these models do not describe the relationship between the body/tissue burden and toxic effects.

Theoretically, the PBTK models yield more exact estimations of the association between the level, duration and pattern of exposure and internal dose than other models. However, the mathematical models are complex, and require information that might not be available. So far, PBTK models have been developed and

validated only for few industrial chemicals, but with the rapid improvements of computational resources, more PBTK models could be developed.

7.4.7 Comparison between time extrapolation tools

In a position paper from 2016, the Australian Institute of Occupational Hygienists (AIOH) (4) exemplified calculations for five exposure standard adjustments, among them three of the major calculation methods described in the previous sections (Brief and Scala, Quebec and pharmacokinetic models) for a range of substances for a site with 12-hour shifts with a roster of days on and off as follows: 4:7, 4:3, 3:1, 3:3. This equates to an average of 14 days worked as 12 hour-shifts over 28 days with a worst case of 4 days on 3 off within the cycle.

As can be seen in Figure 10, there are some dramatic differences in adjusted exposure standards dependent on the adjustment methods used for compounds classified according to the Quebec method (Table 9, Section 7.4.4) into Category I (no adjustment), Category II (daily adjustment), Category III (weekly adjustment) and Category IV (the most conservative, i.e. gives the lowest adjustment factor, of daily and weekly adjustments).

- The Brief and Scala adjustment is the most conservative.
- Pharmacokinetic models are generally more conservative than the Quebec model for Category I compounds such as aluminium fume and some Category III compounds such as asbestos fibres and respiratory crystalline quartz.

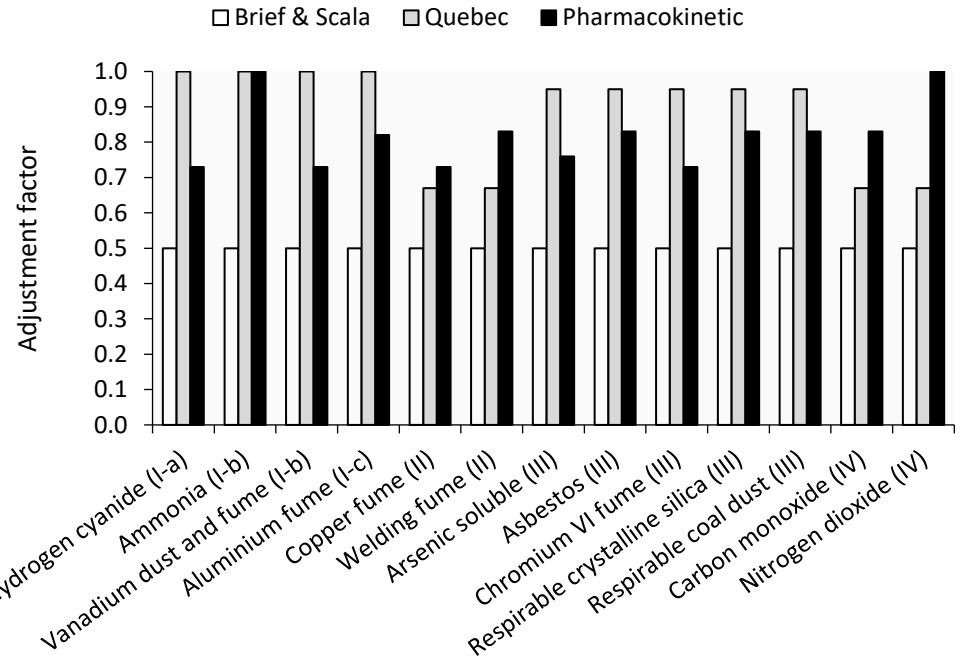

Figure 10. Examples of adjustment factors when applying different time-extrapolation procedures for some dusts, fumes and gases for a work schedule with 14 days of 12-hour shifts over 28 days. Adjustment categories according to the Quebec classification system are given in parenthesis after each compound name (Table 9) [modified from AIOH, 2016 (4)].

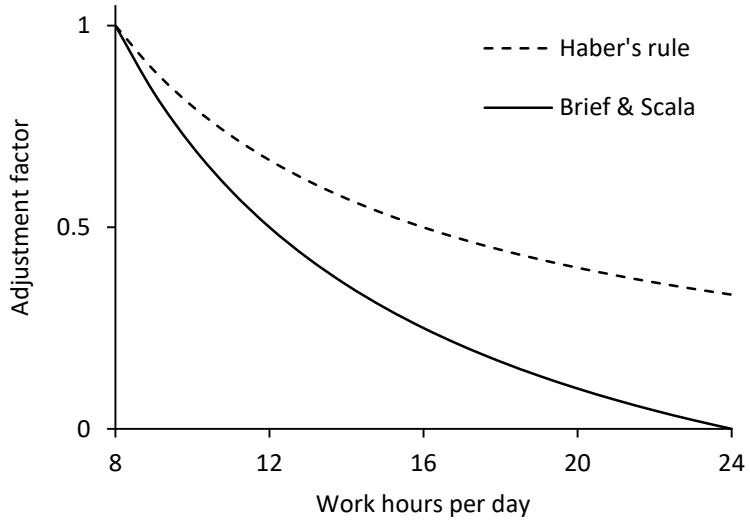

Figure 11. Comparison of adjustment factors according to Haber's rule and the Brief and Scala model.

The adjustment factor in the Brief and Scala model deviates more and more from the Haber's rule model and eventually reaches 0, as working time approaches 24 hours/day or 168 hours/week (Figure 11). The underlying reasoning in the Brief and Scala model of need for time for recovery (when > 8 hours/day or > 40 hours/week) is questionable since there is no need for recovery, provided that the OEL is correctly set at a level that causes no adversity, i.e. below the effect threshold.

7.5 Recommendations on adjustment of OELs

Recommended methods from various national or international bodies to adjust OELs for extended working hours are summarised in Table 10 and briefly described below. So far, there are no recommendations for shift work.

Finland

The Finnish Ministry of Social Affairs and Health (STM) states that there may be reason to use a lower OEL for extended work shifts, e.g. when data on the harmfulness of the substance are limited, if the toxic effect is serious or when the substance is accumulated in the body. In practise, the OEL rarely needs to be lowered if it is based on irritating effects. If the OEL is based on other acute effects or long-term effects and detailed information is lacking, the OEL can in practice be halved or adjusted by using simple formulas. When more detailed information on toxicokinetics is available, a more accurate adjustment factor can be derived. The STM provides examples on how to adjust OELs by using Haber's rule, the Brief and Scala model and the Hickey and Reist model. It is further stated that there is no need for adjustment when the biological half-time is shorter than 3 hours or longer than 400 hours. The biological indicative limit values have with some exceptions been established for a daily exposure of 8 hours and can therefore not always be applied to unusual work shifts (105).

Table 10. Recommended methods for adjust OELs for extended working hours.

Country	Authority, Organisation	Recommendation	Reference
Europe			
Austria	Bundesministerium. Arbeit, Soziales, Gesundheit und Konsumentenschutz	Brief and Scala.	(20)
Denmark	Danish Working Environment Authority	No recommendation.	(8)
European Union	European Chemicals Agency (ECHA)	Modified Haber's rule.	(31)
Finland	Ministry of Social Affairs and Health	Haber's rule, Brief and Scala or pharmacokinetic models.	(105)
Norway	Norwegian Labour Inspection Authority	Brief and Scala.	(7)
	Petroleum Safety Authority Norway	Adjustment factor 0.6 for 12 h.	(93)
Sweden	Swedish Work Environment Authority	Haber's rule.	(9)
Other			
Australia	Safe Work Australia	Brief and Scala.	(96)
	Australian Institute of Occupational Hygienists (AIOH)	Quebec model.	(4)
	Government of Western Australia (mining industry)	Quebec model (mining industry).	(49)
Canada	Canadian Centre for Occupational Health and Safety (CCOHS)	Reference to ACGIHs approach.	(26)
	Government du Québec, Ministère du Travail, de l'Emploi et de la Solidarité sociale	Quebec model.	(55, 77)
United States	Occupational Safety and Health Administration (OSHA)	Lead PEL (50 µg/m^3) = 400 divided by h worked in the day (= Haber's rule).	(84, 85)
	American Conference of Governmental Industrial Hygienists (ACGIH)	Brief and Scala, Quebec model and PBPK models mentioned, but no specific recommendation.	(2)

PBPK: physiologically based pharmacokinetic, PEL: permissible exposure limit.

Norway

The Norwegian Labour Inspection Authority recommends to use the Brief and Scala model to adjust for unusual work schedules and that this model can be used for chemical substances with systemic effect, but cannot be used if the working time is less than 7 hours/day (sic), or is less than 40 hours/week (7).

The Petroleum Safety Authority Norway (PSA) is a government supervisory and administrative agency with regulatory responsibility for safety, the working environment, emergency preparedness and security in the petroleum sector. PSA's supervisory responsibility embraces oil and gas activities on the whole Norwegian

continental shelf in addition to 8 petroleum facilities on land and associated pipeline systems. PSA states that action values and OELs (6) shall be corrected by means of an adjustment factor of 0.6 for a working period not exceeding 12 hours per day for 14 days and with a recovery period 2–3 weeks before the next shift cycle (93). For longer shifts, or if the half-time is known, a more exact adjustment factor can be calculated using the Hickey and Reist (1977) model (33).

Sweden

The Swedish Work Environment Authority states that a standard referencing method may be employed in the event of longer work shifts. The method involves reducing the limit value proportionately through the multiplication of a factor of 8/X, where X is the length of the working day, in hours (9). This corresponds to Haber's rule.

Austria

The Federal Ministry of Social Affairs, Health Care and Consumer Protection states that the Brief and Scala model should be used for adjustment of 8-hour OELs for working hours exceeding 8 hours. STELs do not need to be adjusted. It is further stated that data required for an appropriate pharmacokinetic calculation (e.g. biological excretion rate and half-times) are not always available or difficult to determine and that personal excretion rate differs considerably from typical biological rate depending on a number of factors (e.g. age and gender, bio-transformation enzymes, influence of circadian rhythm). A pharmacokinetic model would therefore not involve any greater accuracy or security for the individual employees, but would involve significantly greater effort (20).

European Union

The former EU Scientific Committee on Occupational Exposure Limits (SCOEL) did not address the issue of unusual working hours and its implications for OELs. However, SCOEL states: "Correct and appropriate use of OELs in practice demands considerable knowledge and expertise, particularly…where the working patterns (e.g. shift system/exposure duration) are non-standard." (98).

Guidance on derivation of derived no-effect levels (DNELs) including DNELs for workers, under the European REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) regulation is given by the European Chemicals Agency (ECHA). ECHA states that if the toxic effect is driven by the total (cumulative) dose, or depends on both total dose and the exposure concentration, concentration-time correction (i.e. time scaling) has to be applied. Time scaling is not appropriate when the toxic effect is mainly driven by the exposure concentration (as for irritation) (31). The guidance names the modified Haber's rule as a useful tool for time scaling, in which the relationship between exposure concentration and exposure duration for a specific effect is exponential.

Canada

The Canadian Centre for Occupational Health and Safety (CCOHS) refers to ACGIH that recommends the Brief and Scala model as a simple model that takes into account the hours worked daily and the periods of rest between them. CCOHS states that one of the shortcomings of the model is that the adjustment factor for a certain amount of worked hours is identical for all chemicals regardless of their individual biological half-times. This assumption may lead to an overestimation of the degree to which the limit should be lowered. The formula is not applicable for: work schedules with less than 7–8 hours/day or less than 40 hours/week, work schedules that involve 24-hour continuous exposure (e.g. in submarines and space shuttles) or certain irritants (26).

Ministère du Travail, de l'Emploi et de la Solidarité sociale in Quebec states that for any work period ≥ 4 hours but < 8 hours or a period > 8 hours but ≤ 16 hours, an adjusted OEL must be established in accordance with the guide (Quebec model) (55). Under no circumstance may the adjusted value be higher than the 8-hour (TWA) OEL (77).

United states

The Occupational Safety and Health Administration (OSHA) has two standards in which the permissible exposure limit (PEL) is adjusted based on the length of the work shift, both of which concern exposure to lead. If an employee is exposed to lead for more than 8 hours in any workday, the OEL (50 µg/m^3), as a TWA for that day, shall be reduced according to the following formula: Maximum OEL (in µg/m^3) = 400 divided by hours worked in the day (Haber's rule) (84, 85).

ACGIH refers to many different methods to adapt existing TLVs to extended work shifts or work weeks, but does not give specific recommendation on which model to select. Thus, they refer to selected readings on this topic, and mention the Brief and Scala model, physiologically based pharmacokinetic (PBPK) models and the Quebec model. ACGIH states that unnecessary exposure of workers should be avoided, even if a model shows such exposures to be "allowable", and that mathematical models should not be used to justify higher-than-necessary exposures (2).

Australia

The governmental body Safe Work Australia (SWA) states that 8-hour TWA exposure standards may need to be adjusted to compensate for the greater exposure during the longer work shift and the decreased recovery time between shifts. 8-Hour TWA exposure standards must not be adjusted upwards for shorter exposure periods or work shifts. Peak limitation or STEL exposure standards must not be adjusted. SWA sets out the major exposure adjustment models, including the Brief and Scala, US OSHA, pharmacokinetic and Quebec models. The use of adjustment models other than the Brief and Scala model should only be done by an appropriately qualified health and safety professional as the use of other models requires a sound understanding of the toxicology and pharmacokinetics of the substance as well as

the rationale for setting the exposure standard. SWA recommends the use of the Brief and Scala model because it is simple to use, takes into account both increased hours of exposure and decreased exposure free time, and is more conservative than other models. When using the Quebec model, exposure standards published by SWA should be used (96).

The Australian Institute of Occupational Hygienists (AIOH) position is that the current guidelines and legislative framework across Australia can lead to inconsistent advice for affected workers. The AIOH recommends moving to a single model based on the Quebec model that references Australian exposure standards, is computer-based, utilises current toxicological information and can provide consistent guidance (4).

The Government of Western Australia, Department of Mines, Industry Regulation and Safety stated in 2019 that to provide current and relevant guidance to the mining industry for adjustment of exposure standards for extended work shifts recommendations made by the AIOH had been adopted and use of the modified Quebec model endorsed (49).

8. NEG recommendations for adjustment of OELs

8.1 Shift work

The time of exposure (day-night) may affect the biotransformation of chemicals, and may thereby affect the toxicity. For some agents, single studies suggest more pronounced effects during night shift compared to day shift exposure, i.e. tiredness and sleepiness from organic solvents, coronary artery disease mortality from carbon disulphide, and impaired lung function from stainless steel strandcasting and endotoxin (Table 6). Organic solvents were also associated with more spontaneous abortions during shift work, including evening, night and rotating shifts. However, insufficient quantitative data are available to allow OEL adjustment for specific chemicals. No suggestions or models for adjustment of OELs for shift work have been published.

Overall, there is currently no scientific basis concerning the adjustment of OELs for shift work.

8.2 Extended working hours

It is not necessary to adjust STELs and ceiling limits, as these are associated with acute rather than chronic exposures.

The strategy for adjustments of OELs (8-hour TWA) in the Quebec method (Section 7.4.4) is recommended as a basis for determining which adjustment method to be used for different categories of substances. This method takes into consideration the biological half-time of the chemical or its metabolite, it is sufficiently conservative and it is relatively easy to apply since it requires little knowledge about the toxicokinetics (only approximate half-times). In short, it is

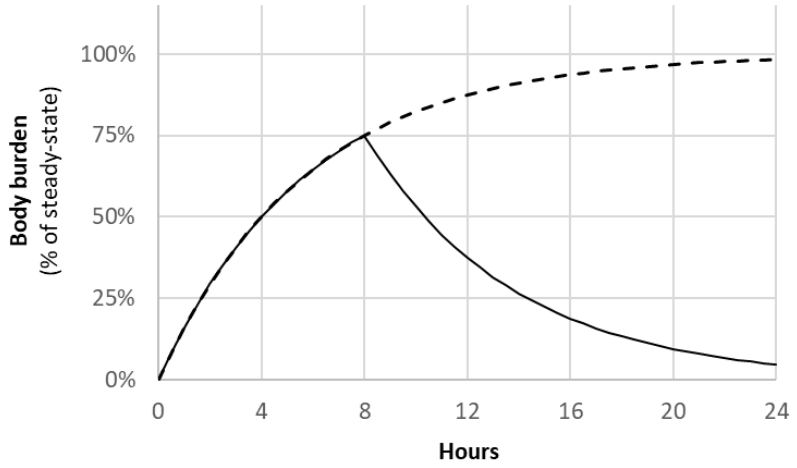

Figure 12. Simulated body burden during an 8-hour workday with constant chemical exposure and an elimination half-time of 4 hours. At the end of the workday, the body burden reaches 75% of that reached at steady-state.

assumed that the intensity of the adverse effect is a function of amount of chemical (or its active metabolite) at the site of action. This amount depends on the exposure intensity and the biological half-time. The half-time is accounted for by grouping chemicals into those that do not accumulate in the body during an 8-hour workday (Category I), those that accumulate during 8 hours (Category II) or those that accumulate over longer exposure times (Category III).

The Brief and Scala method (Section 7.4.1) is even easier to apply and tends to be even more conservative (Section 7.4.7 and Figure 10). However, the need for time for recovery is questionable as recovery is not needed if the OEL is correctly set and complied with, i.e. at a level causing no adverse effect.

Category I. No adjustment

No adjustment for number of work hours even when exceeding 8 hours per day. Substances where acute health effects drive the OEL. Examples in this category include irritating/malodourous substances and simple asphyxiants, where the effect develops within minutes. Substances with half-times below 4 hours are also included if there is no build-up of toxic metabolite(s) or effect(s). A half-time of 4 hours implies that 8 hours of exposure results in 75% of the body burden that would be reached after infinite exposure (steady-state) (Figure 12).

Category II. Daily adjustment

Adjustment for number of work hours when exceeding 8 hours per day. Applies to substances that produce effects following short-term exposure (hours-days) and/or with half-times between 4 hours and 3 days, e.g. acetonitrile. The daily adjustment serves to prevent excessive accumulation during workdays exceeding 8 hours. A half-time of 3 days implies that one week of exposure results in 80% of the body burden reached after several weeks of exposure (assuming 8 hours per day and 5 days per week, Figure 13).

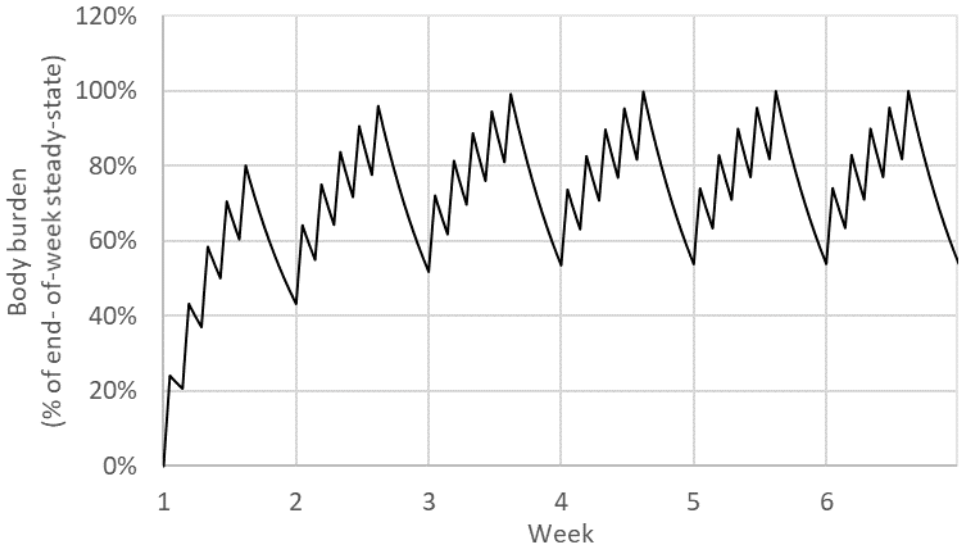

Figure 13. Simulated body burden over 6 weeks with constant chemical exposure 8 hours/day, 5 days/week and an elimination half-time of 3 days. At the end of the first week of exposure, the body burden reaches 80% of that reached after several weeks of exposure.

The daily adjusted OEL is calculated by applying Haber's rule as:

Adjusted OEL = OEL × 8 / h_d,

where h_d is the number of work hours per day.

No upward adjustment is made for workdays shorter than 8 hours.

Category III. Weekly adjustment
Adjustment for number of work hours per week when exceeding 40 hours. Applies to substances that produce effects following long-term exposure (several days-years) and/or with half-times above 3 days, e.g. lead, and for substances that produce long-lasting or cumulative effects, e.g. mutagens. The adjustment accounts for the cumulative increase in body burden during exposure to such substances (Figure 14).

The weekly adjusted OEL is calculated by applying Haber's rule as:

Adjusted OEL = OEL × 40 / h_{wk},

where h_{wk} is the number of work hours per week.

No upward adjustment is made for work weeks shorter than 40 hours.

Category IV. Daily or weekly adjustment
Applies to substances where there is uncertainty regarding the toxicokinetics and toxicodynamics. In such cases the most conservative of categories II and III, i.e. the one leading to the lowest adjusted OEL, should be applied.

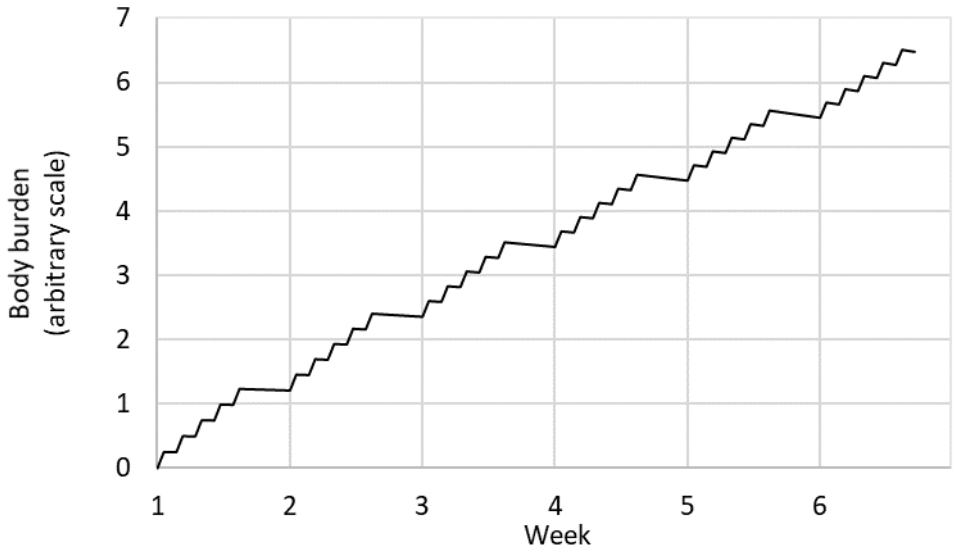

Figure 14. Simulated body burden over 6 weeks with constant chemical exposure 8 hours/day, 5 days/week and an elimination half-time of 3 months. The increase during work periods is practically linear, illustrating that the body burden is practically proportional to the total number of work hours.

For choice of adjustment category, it may be helpful to consult Appendix IV in the IRSST report (55). The information is also available online by chemical name (56).

9. Research needs

So far, there are few published studies in which the main objective is assessment of effects of the combined exposure to shift work and chemicals. Research is recommended in the following areas:

- Statistics on types of occupations and industries in which exposure to chemicals occurs in combination with unusual working hours.
- Studies focusing on classes of chemicals with effects relevant for shift work. Of particular interest are chemicals metabolised by enzymes with circadian enzymatic activity, and further development of pharmacokinetic modelling of body burden of these chemicals.
- Epidemiological studies related to chronotoxicity, with well documented exposure measurements of both shift work and chemicals, for example of pharmaceutical and health care personnel exposed to cytostatics and working night shifts.
- Animal studies with the most relevant exposure route (e.g. inhalation), to better understand mechanisms of combined effects of shift work and chemicals.
- Individual susceptibility to shift work (e.g. effects on immune system, lung function, metabolic rates) in ways that might affect interactions with chemical exposure.

These research needs have similarities with the recommendations provided in a consensus paper developed by the Working Time Society, commissioned by the International Commission on Occupational Health (102).

10. Summary

Lie JA, Zienolddiny-Narui S, Bråtveit M. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals.* 155. Occupational chemical exposures in combination with unusual working hours. Arbete och Hälsa 2023;57(2):1-86.

A significant proportion of the work force is employed in unusual work schedules. The combined effects of working hours and chemical agents at the workplace may depend on the duration and/or timing of exposure. However, occupational exposure limits (OELs) usually assume working day-time, an 8-hour workday, 5 days/week and a 40-hour work week. The aims of this document were to review the scientific support for a combined effect of unusual working hours (shift work or extended working hours) and chemical exposure and, to the extent possible provide recommendations for down-adjustment of the OEL to account for unusual working hours.

Animal data from chronopharmacological studies suggest that the time of exposure (day-night) may affect the biotransformation and toxicity of chemicals. A few epidemiological studies, i.e. regarding effects of dust and endotoxin on lung function, effects of acetone on sleep quality and tiredness, effects of carbon disulphide on coronary artery disease and effects of chemicals on spontaneous abortion, suggest more pronounced effects during night shifts compared to day shift exposure. However, the reviewed data are considered insufficient to conclude on recommendations for OEL adjustment for shift work.

The Quebec method is recommended to adjust for extended working hours. Each chemical is assigned in categories based on the toxic effect. No adjustment is applied for ceiling values, short-term exposure limits and limit values based on asphyxiation, irritation or malodour. For other substances producing effects following short- or long-term exposure, the method is based on Haber's rule and the type of adverse effect.

Keywords: chemical exposure, combined effect, extended working hours, occupational exposure limit, review, shift work, toxicity, unusual working hours.

11. Summary in Norwegian

Lie JA, Zienolddiny-Narui S, Bråtveit M. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals.* 155. Occupational chemical exposures in combination with unusual working hours. Arbete och Hälsa 2023;57(2):1-86.

En betydelig andel av arbeidsstyrken er ansatt i uvanlige arbeidstidsordninger. Den kombinerte effekten av arbeidstid og kjemiske stoffer på arbeidsplassen kan være avhengig av eksponeringens varighet og/eller tidspunkt. Imidlertid gjelder yrkeshygieniske grenseverdier (GV) vanligvis for arbeid på dagtid, 8-timers arbeidsdag, 5 dager i uken og en 40-timers arbeidsuke. Målsettingen for dette dokumentet var å gjennomgå vitenskapelig dokumentasjon for en kombinert effekt av uvanlige arbeidstidsordninger (skiftarbeid eller utvidet arbeidstid) og kjemisk eksponering og, i den grad det er mulig, gi anbefalinger for nedjustering av GV for å ta høyde for uvanlige arbeidstidsordninger.

Data fra kronofarmakologiske studier på dyr tyder på at eksponeringstidspunktet (dag-natt) kan påvirke biotransformasjonen og toksisiteten av kjemikalier. Et fåtall epidemiologiske studier, dvs. effekter av støv og endotoksin på lungefunksjon, effekter av aceton på søvnkvalitet og tretthet, effekter av karbondisulfid på koronarsykdom og effekten av kjemikalier på spontanabort antyder mer uttalte effekter under nattskift sammenlignet med eksponering på dagskift. De gjennomgåtte dataene blir imidlertid ansett som utilstrekkelige til å konkludere med anbefalinger for GV-justering for skiftarbeid.

Quebec-metoden anbefales for å justere for utvidet arbeidstid. Hvert kjemikalie er fordelt på kategorier basert på den toksiske effekten. Det gjøres ingen justering for takverdier, korttidseksponeringsgrenser, og grenseverdier basert på kvelning, irritasjon eller vond lukt. For andre stoffer som gir effekter etter kort- eller langtidseksponering, er metoden basert på Habers regel og type effekt.

Nøkkelord: kjemisk eksponering, kombinasjonseffekt, review, skiftarbeid, toksisitet, utvidet arbeidstid, uvanlige arbeidstider, yrkeshygieniske grenseverdier.

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13. Data bases and search strategy

In the search for literature the following data bases were used:

Embase
Medline
OSH
SCOPUS
Toxicology
Web of Science
ProQuest Health and Safety

Searches were performed using terms related to unusual working hours combined with terms related to chemical exposures and adverse effects.

Terms related to unusual working hours included (but were not limited to):

Long work hours
Night work
Overtime
Shift work
Work hour(s)
Work schedule(s)

Terms related to chemical exposure included (but were not limited to):

Benzene
BTEX
Carcinogen(s)
Ethylbenzene(s)
Hazardous substance(s)
Pollutant(s)
Polycyclic aromatic hydrocarbon(s)
Solvent(s)
Toluene
Xylene(s)

A separate search was made on cytostatics (the resulting papers addressed treatment of patients and none were considered relevant for occupational exposure):

Anticancer
Anticarcinogen
Antineoplastic drug(s)/agent(s)
Antitumor
Chemotherapy(ies)
Cytostatic(s)

Terms related to adverse effects included (but was not limited to):

Adverse effect

Circadian rhythm/disruption
Metabolism
Pharmacology
Pharmacokinetic(s)
Poisoning(s)
Toxic
Toxicity(ies)

The searches were limited to studies published in English. The last search was performed in November 2021.

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Appendix 1. Previous NEG criteria documents

NEG documents published in the scientific series Arbete och Hälsa (Work and Health).

Substance/Agent/Endpoint	Arbete och Hälsa issue
Acetonitrile	1989:22, 1989:37*
Acid aerosols, inorganic	1992:33, 1993:1*
Acrylonitrile	1985:4
Allyl alcohol	1986:8
Aluminium and aluminium compounds	1992:45, 1993:1*, 2011;45(7)*D
Ammonia	1986:31, 2005:13*
Antimony	1998:11*
Arsenic, inorganic	1981:22, 1991:9, 1991:50*
Arsine	1986:41
Asbestos	1982:29
Benomyl	1984:28
Benzene	1981:11
1,2,3-Benzotriazole	2000:24*D
Boric acid, Borax	1980:13
1,3-Butadiene	1994:36*, 1994:42
1-Butanol	1980:20
γ-Butyrolactone	2004:7*D
Cadmium	1981:29, 1992:26, 1993:1*
7/8 Carbon chain aliphatic monoketones	1990:2*D
Carbon monoxide	1980:8, 2012;46(7)*
Carbon nanotubes	2013;47(5)*
Carcinogens, Approaches for the setting of occupational exposure limits (OELs)	2022;56(2)*
Cardiovascular disease, Occupational chemical exposures and	2020;54(2)*
Ceramic Fibres, Refractory	1996:30*, 1998:20
Chloramines, Inorganic	2019;53(2)*
Chlorine, Chlorine dioxide	1980:6
Chloromequat chloride	1984:36
4-Chloro-2-methylphenoxy acetic acid	1981:14
Chlorophenols	1984:46
Chlorotrimethylsilane	2002:2
Chromium	1979:33
Cobalt	1982:16, 1994:39*, 1994:42
Copper	1980:21
Creosote	1988:13, 1988:33*
Cyanoacrylates	1995:25*, 1995:27
Cyclic acid anhydrides	2004:15*D
Cyclohexanone, Cyclopentanone	1985:42
n-Decane	1987:25, 1987:40*
Deodorized kerosene	1985:24
Diacetone alcohol	1989:4, 1989:37*
Dichlorobenzenes	1998:4*, 1998:20
Diesel engine exhaust	2016;49(6)*D

NEG documents published in the scientific series Arbete och Hälsa (Work and Health).

Substance/Agent/Endpoint	Arbete och Hälsa issue
Diesel exhaust	1993:34, 1993:35*
Diethylamine	1994:23*, 1994:42
2-Diethylaminoethanol	1994:25*N
Diethylenetriamine	1994:23*, 1994:42
Diisocyanates	1979:34, 1985:19
Dimethylamine	1994:23*, 1994:42
Dimethyldithiocarbamates	1990:26, 1991:2*
Dimethylethylamine	1991:26, 1991:50*
Dimethylformamide	1983:28
Dimethylsulfoxide	1991:37, 1991:50*
Dioxane	1982:6
Endotoxins	2011;45(4)*D
Enzymes, industrial	1994:28*, 1994:42
Epichlorohydrin	1981:10
Ethyl acetate	1990:35*
Ethylbenzene	1986:19
Ethylenediamine	1994:23*, 1994:42
Ethylenebisdithiocarbamates and Ethylenethiourea	1993:24, 1993:35*
Ethylene glycol	1980:14
Ethylene glycol monoalkyl ethers	1985:34
Ethylene oxide	1982:7
Ethyl ether	1992:30* N
2-Ethylhexanoic acid	1994:31*, 1994:42
Flour dust	1996:27*, 1998:20
Formaldehyde	1978:21, 1982:27, 2003:11*D
Fungal spores	2006:21*
Furfuryl alcohol	1984:24
Gasoline	1984:7
Glutaraldehyde	1997:20*D, 1998:20
Glyoxal	1995:2*, 1995:27
Halothane	1984:17
Hearing impairment, Occupational exposure to chemicals and	2010;44(4)*
n-Hexane	1980:19, 1986:20
Hydrazine, Hydrazine salts	1985:6
Hydrogen fluoride	1983:7
Hydrogen sulphide	1982:31, 2001:14*D
Hydroquinone	1989:15, 1989:37*
Industrial enzymes	1994:28*
Isoflurane, sevoflurane and desflurane	2009;43(9)*
Isophorone	1991:14, 1991:50*
Isopropanol	1980:18
Lead, inorganic	1979:24, 1992:43, 1993:1*
Limonene	1993:14, 1993:35*
Lithium and lithium compounds	2002:16*
Manganese	1982:10

NEG documents published in the scientific series Arbete och Hälsa (Work and Health).

Substance/Agent/Endpoint	Arbete och Hälsa issue
Mercury, inorganic	1985:20
Methacrylates	1983:21
Methanol	1984:41
Methyl bromide	1987:18, 1987:40*
Methyl chloride	1992:27*D
Methyl chloroform	1981:12
Methylcyclopentadienyl manganese tricarbonyl	1982:10
Methylene chloride	1979:15, 1987:29, 1987:40*
Methyl ethyl ketone	1983:25
Methyl formate	1989:29, 1989:37*
Methyl isobutyl ketone	1988:20, 1988:33*
Methyl methacrylate	1991:36*D
N-Methyl-2-pyrrolidone	1994:40*, 1994:42
Methyl-tert-butyl ether	1994:22*D
Microbial volatile organic compounds (MVOCs)	2006:13*
Microorganisms	1991:44, 1991:50*
Mineral fibers	1981:26
Nickel	1981:28, 1995:26*, 1995:27
Nitrilotriacetic acid	1989:16, 1989:37*
Nitroalkanes	1988:29, 1988:33*
Nitrogen oxides	1983:28
N-Nitroso compounds	1990:33, 1991:2*
Nitrous oxide	1982:20
Oil mist	1985:13
Organic acid anhydrides	1990:48, 1991:2*
Ozone	1986:28
Paper dust	1989:30, 1989:37*
Penicillins	2004:6*
Permethrin	1982:22
Petrol	1984:7
Phenol	1984:33
Phosphate triesters with flame retardant properties	2010;44(6)*
Phthalate esters	1982:12
Platinum	1997:14*D, 1998:20
Polychlorinated biphenyls (PCBs)	2012;46(1)*
Polyethylene, Thermal degradation products in the processing of plastics	1998:12*
Polypropylene, Thermal degradation products in the processing of plastics	1998:12*
Polystyrene, Thermal degradation products in the processing of plastics	1998:12*
Polyvinylchloride, Thermal degradation products in the processing of plastics	1998:12*
Polytetrafluoroethylene, Thermal degradation products in the processing of plastics	1998:12*
Propene	1995:7*, 1995:27

NEG documents published in the scientific series Arbete och Hälsa (Work and Health).

Substance/Agent/Endpoint	Arbete och Hälsa issue
Propylene glycol	1983:27
Propylene glycol ethers and their acetates	1990:32*N
Propylene oxide	1985:23
Refined petroleum solvents	1982:21
Refractory Ceramic Fibres	1996:30*
Selenium	1992:35, 1993:1*
Silica, crystalline	1993:2, 1993:35*
Silicon carbide	2018;52(1)*
Skin exposure to chemicals, Occupational	2018;52(3)*
Styrene	1979:14, 1990:49*, 1991:2
Sulphur dioxide	1984:18
Sulphuric, hydrochloric, nitric and phosphoric acids	2009;43(7)*
Synthetic pyretroids	1982:22
Tetrachloroethane	1996:28*D
Tetrachloroethylene	1979:25, 2003:14*D
Thermal degradation products of plastics	1998:12*
Thiurams	1990:26, 1991:2*
Tin and inorganic tin compounds	2002:10*D
Toluene	1979:5, 1989:3, 1989:37*, 2000:19*
1,1,1-Trichloroethane	1981:12
Trichloroethylene	1979:13, 1991:43, 1991:50*
Triglycidyl isocyanurate	2001:18*
n-Undecane	1987:25, 1987:40*
Vanadium	1982:18
Vinyl acetate	1988:26, 1988:33*
Vinyl chloride	1986:17
Welding gases and fumes	1990:28, 1991:2*
White spirit	1986:1
Wood dust	1987:36
Xylene	1979:35
Zinc	1981:13

* : in English, remaining documents are in a Scandinavian language.
D: collaboration with the Dutch Expert Committee on Occupational Safety (DECOS).
N: collaboration with the US National Institute for Occupational Safety and Health (NIOSH).

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