National Research Centre
for the Working Environment

Pyridine

Scientific basis for setting a health-based occupational exposure limit

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Videnskabelig dokumentation for helbredsbaseret grænseværdi

Sarah Søs Poulsen, Anne Thoustrup Saber, Alicja Mortensen, Pernille Danielsen, Niels Hadrup and Ulla Vogel

The National Research Centre for the Working Environment, Copenhagen 2025

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Foreword

At request of the Danish Working Environment Authority, a working group at the National Research Centre for the Working Environment (NFA) has made this documentation to establish a health-based OEL for pyridine.

The OEL derivation and risk assessment methodology of this report follows the guidelines outlined by REACH guidance documents (ECHA, 2012b, 2017, 2019; ECHA/RAC-SCOEL, 2017a).

The working group wishes to thank Chief Toxicologist Poul Bo Larsen, DHI, Denmark, for critically reviewing the report.

Copenhagen, February 2025

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Abbreviations

AF	Assessment factor
DECOS	Dutch Expert Committee on Occupational Safety
DNEL	Derived No Effect Level
ECHA	European Chemicals Agency
IARC	World Health Organization's International Agency for Research on Cancer
LOAEL	Lowest Observed Adverse Effect Level
NFA	National Research Centre for the Working Environment
NTP	National Toxicology Program
NOAEL	No Observed Adverse Effect Level
OEL	Occupational Exposure Limit
RR	Relative Risk
RIVM	The National Institute of Public Health and the Environment
SCOEL	The Scientific Committee on Occupational Exposure Limits

Executive summary

In this report, a working group at the National Research Centre for the Working Environment reviewed data relevant to assess the hazard of pyridine and calculated health-based occupational exposure limits (OELs) based on data from animal studies.

The current Danish OEL is 15 mg/m^3 for pyridine.

Pyridine is a heterocyclic organic compound, which is an effective, basic solvent and as it is relatively unreactive, it serves as a good acid scavenger. As a result, pyridine is widely used as a solvent in organic chemistry but is also used for several other purposes.

For the literature search the present working group used the same search profiles as a recently published report on pyridine mutagenicity and carcinogenicity by The National Institute of Public Health and the Environment (RIVM) to identify new studies published after the search performed by RIVM (Chen & Zijtveld, 2021). However, as the current working group not solely investigate pyridine mutagenicity and carcinogenicity, a second broader search was performed to identify other toxicological effects.

The present working group evaluated the relevant literature on pyridine from both epidemiological and animal studies. However, since no suitable human studies were identified, endpoints were based on animal studies. The present working group furthermore notes that no human studies on reproductive and developmental effects were identified.

IARC has classified pyridine as a group 2B carcinogen (IARC, 2019a), but concludes that the evidence of genotoxicity is weak.

The current working group regards pyridine-induced liver cancer and lesions in the nose as critical effects. The current working group has calculated health-based OELs based on cancer data from 2 year oral animal studies from the National Toxicology Program (NTP, 2000) and in addition for lesions in the nose based on a 4-day inhalation study in rats (Nikula & Lewis, 1994).

The evidence for a non-threshold mechanism of action for cancer is weak. However, since a non-threshold mechanism-of-action for pyridine-induced cancer cannot be excluded, the present working group considers pyridine-induced cancer in mice as non-threshold mechanism. The current working group calculated an excess of cancer incidences for 1:1,000 at 57 μg/m^3 and 1:10,000 at 5.7 μg/m^3. However, because of the weak evidence for pyridine-induced genotoxicity, the present working group chose in addition to present calculations where cancer is considered a threshold effect. When considered a threshold effect, the calculated DNEL for cancer is 40 μg/m^3.

The present working group considers pyridine-induced nose lesions in rats as a threshold effect. A DNEL was calculated based on a 4-day inhalation study in rats. This results in a DNEL at 11 μg/m^3 for olfactory mucosal lesions.

The present working group notes that the study on changes in the nose mucosa is based inhalation exposure which is the occupationally relevant exposure route while the cancer risk estimates are based on oral exposure of mice. This means that the risk estimates based on the cancer study come with additional uncertainties due to 1) the use of a different exposure route than what is relevant in an occupational setting, and 2) an unclear mechanism-of-action for genotoxic effects.

On that background the present working group is of the opinion that both risk estimates should be taken into account. These are listed in the table below:

Table. Overview of final risk estimates

Threshold effects	Study type	Critical effect	DNEL
	Short-term animal study	Olfactory mucosal lesions	11 μg/m^3
Non-threshold effects			Risk levels
	Long-term animal study	Cancer	1: 1000 at 57 μg/m^3
			1:10,000 at 5.7 μg/m^3
			1:100,000 at 0.57 μg/m^3

The working group notes that the odour threshold of pyridine (0.2 ppm (650 μg/m^3) (SCOEL, 2004)) is above the suggested risk estimates and DNEL.

Finally, the current working group recommends a skin notation for pyridine due to its rapid absorption through intact skin and its water and lipid solubility (Reinhardt & Brittelli, 1981) and ((Santodonato, 1985) as referred by (DECOS, 1993)).

Dansk sammenfatning

Ved fastsættelse af grænseværdier i arbejdsmiljøet indgår en række hensyn. Det drejer sig om helbredsrisikoen, men også tekniske og samfundsmæssige hensyn.

I NFA's arbejde med grænseværdidokumentation anvendes risikoestimater, som er et teoretisk mål for hvor mange, der ved daglig udsættelse for stoffet ved grænseværdien efter et helt arbejdsliv (typisk efter 40-45 år) vil blive syge. I disse beregninger, er der *ikke* taget hensyn til personlige værnemidler eller andre kendte foranstaltninger til beskyttelse mod eksponering.

NFA udarbejder dokumentation for helbredsbaserede grænseværdier. Der tages udgangspunkt i publiceret systematisk litteraturgennemgang af epidemiologiske studier, dyrestudier og cellestudier af sammenhængen mellem udsættelse og risiko for forskellige helbredsudfald og de biologiske virkningsmekanismer. På baggrund af dette videnskabelige arbejde beregnes risikoestimaterne.

Dokumentation for helbredsbaserede grænseværdier vil sammen med de tekniske og samfundsmæssige betragtninger ligge til grund for forhandlinger mellem arbejdsmarkedets parter om endelig fastsættelse af grænseværdierne.

I denne rapport vurderer en arbejdsgruppe ved NFA data, der er relevante for at evaluere faren ved udsættelse for pyridine, og beregner helbredsbaserede græseværdier for disse i arbejdsmiljøet. Beregningerne baseres på data fra dyreforsøg. Den nuværende danske grænseværdi for pyridin i arbejdsmiljøet er 15 mg/m^3.

Pyridin er en heterocyklisk organisk forbindelse, der fungerer som et effektivt, basisk opløsningsmiddel. Da det er relativt inert, fungerer det desuden som en god syrefanger. Som følge heraf anvendes pyridin bredt som opløsningsmiddel i organisk kemi, men det har også flere andre anvendelser.

Til litteratursøgningen anvendte den nuværende arbejdsgruppe de samme søgeprofiler som en nyligt offentliggjort rapport fra The National Institute of Public Health and the Environment (RIVM) om pyridins mutagenicitet og kræftfremkaldende egenskaber for at identificere nye studier offentliggjort efter den søgning, der blev udført af RIVM (Chen & Zijtveld, 2021). Da den nuværende arbejdsgruppe imidlertid ikke udelukkende undersøgte pyridins mutagenicitet og kræftfremkaldende egenskaber, blev en anden bredere søgning udført for at identificere andre toksikologiske effekter.

Den nuværende arbejdsgruppe har evalueret den relevante litteratur om pyridin fra både epidemiologiske og dyrestudier. Da der ikke blev identificeret egnede humane studier, blev endepunkterne baseret på dyreforsøg. Arbejdsgruppen bemærker desuden, at der ikke blev identificeret humane studier om reproduktions- og udviklingseffekter.

IARC har klassificeret pyridin som en gruppe 2B-karcinogen (IARC, 2019a), men konkluderer, at evidensen for genotoksicitet er svag.

Den nuværende arbejdsgruppe betragter pyridin-induceret leverkræft og læsioner i næsen som kritiske effekter. Arbejdsgruppen har beregnet sundhedsbaserede grænseværdier baseret på kræftdata fra 2-årige orale dyreforsøg fra National Toxicology Program (NTP, 2000) og desuden for næselæsioner baseret på et 4-dages inhalationsstudie i rotter (Nikula & Lewis, 1994).

Evidensen for en ikke-tærskel virkningsmekanisme for kræft er svag. Da en ikke-tærskel virkningsmekanisme for pyridin-induceret kræft dog ikke helt kan udelukkes, betragter arbejdsgruppen pyridin-induceret kræft hos mus som en ikke-tærskel mekanisme. Den nuværende arbejdsgruppe beregnede en forøget risiko for kræfttilfælde på 1:1.000 ved 57 μg/m³ og 1:10.000 ved 5,7 μg/m³. På grund af den svage evidens for pyridin-induceret genotoksicitet, har arbejdsgruppen også valgt at præsentere beregninger, hvor kræft betragtes som en tærskeleffekt. Når kræft betragtes som en tærskeleffekt, er den beregnede DNEL 40 μg/m³.

Den nuværende arbejdsgruppe betragter pyridin-inducerede næselæsioner hos rotter som en tærskeleffekt. En DNEL blev beregnet baseret på et 4-dages inhalationsstudie i rotter, hvilket resulterer i en DNEL på 11 μg/m³ for olfaktoriske slimhindelæsioner.

Arbejdsgruppen bemærker, at studiet om ændringer i næseslimhinden er baseret på inhalationseksponering, hvilket er den erhvervsmæssigt relevante eksponeringsvej, mens kræftrisikoestimaterne er baseret på oral eksponering hos mus. Dette betyder, at risikoestimaterne baseret på kræftstudiet er er behæftet med yderligere usikkerheder på grund af: 1) anvendelsen af en anden eksponeringsvej end den, der er relevant i en arbejdsmæssig kontekst, og 2) en uklar virkningsmekanisme for genotoksiske effekter.

På baggrund af dette er den nuværende arbejdsgruppe af den opfattelse, at begge risikoestimater bør tages i betragtning. Disse er angivet i tabellen på næste side.

Tabel. Oversigt over endelige risikoestimater

Tærskel-effekter	Studietype	Kritisk effekt	DNEL
	Korttids-dyrestudie	Olfaktoriske slimhindelæsioner	11 μg/m³
Ikke-tærskeleffekter			Risikoniveauer
	Langtids-dyrestudie	Kræft	1: 1.000 ved 57 μg/m³
			1:10.000 ved 5,7 μg/m³
			1:100.000 ved 0,57 μg/m³

Arbejdsgruppen bemærker, at lugttærsklen for pyridin (0,2 ppm (650 μg/m³) (SCOEL, 2004)) er højere end de foreslåede risikoestimater og DNEL.

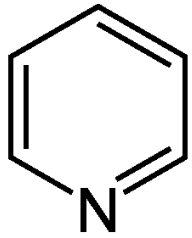
Endelig anbefaler den nuværende arbejdsgruppe en hudnotation for pyridin på grund af dets hurtige absorption gennem intakt hud samt dets vand- og fedtopløselighed (Reinhardt & Brittelli, 1981) og ((Santodonato, 1985) som refereret af (DECOS, 1993)).

Introduction

Pyridine

Substance identification

CAS no.: 110-86-1
EC/List No.: 203-809-9
CAS name: Pyridine
IUPAC systematic name: Pyridine
Synonyms: Azabenzene; azine
Molecular formula: C_5H_5N



Chemical and physical properties

Relative molecular mass: 79.1
Boiling point: 115 °C
Melting point: −42 °C
Density: 0.9819 g/cm^3 at 20 °C
Solubility: Miscible with water, acetone, benzene, chloroform, diethyl ether, and ethanol. Solubility in water is 1000 g/L at 20 °C
Vapour pressure: 2.66 kPa at 25 °C
Vapour density: 2.73
Flash point: 20 °C
pH value: 8.5 (0.2 M solution in water)
Self-ignition temperature: 900 °C at standard atmospheric pressure of 101.3 kPa
Specific gravity: 0.98 at 20 °C
Partition coefficient n-octanol/water (P): 0.64 at 20 °C
Dissociation constant: pKa = 5.23
Odour threshold: 0.2 ppm (0.65 mg/m^3)
Conversion factor: 1 ppm = 3.24 mg/m^3

EU classification:
Harmonised EU classification:
Flammable liquids (Category 2), H225
Acute toxicity, Oral (Category 4), H302
Acute toxicity, Inhalation (Category 4), H332
Acute toxicity, Dermal (Category 4), H312

Additional classification in REACH registration:
Skin irritation (Category 2), H315
Eye irritation (Category 2), H319

Data on physicochemical properties have been collected from previous reports (Chen & Zijtveld, 2021; IARC, 2019a, b; PubChem, 2025; SCOEL, 2004).

Manufacture and use

Pyridine is a heterocyclic organic compound, which presents as a volatile, colourless (or slightly yellowish) liquid with a disagreeable odour. The odour threshold of pyridine is reported to be about 0.2 ppm (0.65 mg/m^3)(SCOEL, 2004).
It has historically been extracted from coal tar or obtained as a by-product of coal gasification. Both processes were inefficient and time-consuming due to low content of pyridine in coal tar and to a necessary multistage purification process ((Gossauer, 2006) as referred by (IARC, 2019a, b). Today, pyridine is almost solely produced by synthesis (Shimizu et al., 2000). One of the main methods in use is the Tchichibabin synthesis (Tschitschibabin, 1924) as referred by (IARC, 2019a), as it is suitable for mass production. It involves a condensation reaction of acetaldehyde and formaldehyde with ammonia, usually carried out at 350–550 °C and at a space velocity of 500–1000 h^{-1} in the presence of a solid acid catalyst. In addition, low commercial value by-products of pyridine base synthesis, such as alkylpyridines, can be converted into useful pyridine bases by dealkylation. Beside the Tchichibabin synthesis, pyridine can also be prepared from cyclopentadiene by ammoxidation, or from 2-pentenenitrile by cyclization and dehydrogenation. These synthesis processes and others are described in detail by Shimizu and colleagues (Shimizu et al., 2000)).

The yearly production volume of pyridine in Denmark is 21.1 tons (AT, 2025). In Europe, pyridine is marketed at a yearly tonnage level of 1000 – 10 000 tonnes (ECHA, 2023). Pyridine is an effective, basic solvent and as it is relatively unreactive, it serves as a good acid scavenger. As a result, pyridine is widely used as a solvent in organic chemistry, for example for paint, rubber, polycarbonate resins, textile water repellents, and for acylation and dehydrochlorination reactions. It is also used as a denaturant in alcohol and antifreeze mixtures, and as an intermediate in the manufacture of insecticides, herbicides, and fungicides (NTP, 2000). Pyridine is also used in the production of substituted pyridines, of piperidine, and as an intermediate and solvent in the preparation of vitamins and drugs, dyes, textile water repellents, and flavouring agents in food (Chen & Zijtveld, 2021; IARC, 2019a; SCOEL, 2004). The main pyridine producing country is China, followed by India. Agricultural chemicals, mainly the non-selective contact herbicide paraquat, account for most consumption of pyridine (S&P Global, 2018).

Literature search

The National Institute of Public Health and the Environment (RIVM) published in 2021 a letter report on pyridine mutagenicity and carcinogenicity (Chen & Zijtveld, 2021). In this report they published their search profiles for different literature databases. The

present report will utilize these profiles to identify new studies published after the search performed by RIVM. However, as the current working group not solely investigate pyridine mutagenicity and carcinogenicity, a second broader search was performed to catch other toxicological effects. Further details on the literature search are described in appendix A.

Toxicokinetics

Uptake, distribution and excretion

Very little information is available on uptake and distribution in humans, and no data is available on airborne exposure. In a very small oral study with two male volunteers receiving 3.4 mg [^{14}C]-pyridine in orange juice (approximately 0.05 mg/kg bw), about 65% and 68% was recovered in the urine 24 hours after exposure, mostly in the form of the metabolite pyridine-N-oxide (D'Souza et al., 1980; Damani et al., 1982).

As for humans, no biodistribution studies following inhalation exposure in animal exist.

However, the absorption, distribution, and excretion of pyridine have been described after either intraperitoneal injection or oral exposure in different experimental animal species. This was summarized by IARC as follows:

"As in humans, pyridine is absorbed by various tissues in a dose-dependent manner, but there is no tissue accumulation due to rapid elimination in urine, faeces, and exhaled breath. Significant species- and dose-dependent differences have been reported. For example, urinary excretion of pyridine N-oxide after mice, hamsters, rats, guinea-pigs, rabbits, and ferrets were given pyridine by intraperitoneal injection varied from 10% of the dose in rats to almost 40% in mice and guinea-pigs. A comparison of urinary excretion in several species (i.e. rats, guinea-pigs, mice, gerbils, hamsters, rabbits, and cats) given intraperitoneal injections of [14C]-labelled pyridine (7 mg/kg bw) showed marked species differences in the extent of recovery, ranging from 48% of the total dose in rats to 75% in cats. In the same study, comparisons of urinary excretion after either oral or intraperitoneal administration revealed similar rates of recovery for a given species regardless of route of administration. This observation is consistent with the rapid and virtually complete absorption of pyridine regardless of route of administration." (IARC, 2019a)

Metabolism

Very little information is available on the metabolism of pyridine in humans, and no data is available for airborne exposure. In a very small oral study, two male volunteers received pyridine at a dose of 3.4 mg of [14C]-labelled pyridine (~0.05 mg/kg bw) in orange juice (D'Souza et al., 1980; Damani et al., 1982). Twenty-four hours after exposure, 65% and 68% of the dose was recovered in urine of the two volunteers. Two main metabolites were identified: pyridine N-oxide, which accounted for 32% of the dose, and N-methylpyridinium ion, accounting for 5.5 and 12% of the dose, respectively, for the two volunteers. Approximately 25% of the dose was not characterized (D'Souza et al., 1980; Damani et al., 1982).

Most knowledge of pyridine metabolism comes from animal studies. Pyridine is initially metabolised by cytochrome P450 2E1 (CYP2E1) through oxidation at the nitrogen atom, resulting in pyridine-N-oxide, which is generally the predominant metabolite recovered in the urine in the species studied, or at the carbon atoms of the ring, resulting in 2- and 4-pyridone and 3-hydroxypyridine (See figure 1). Other CYPs types, as CYP2B1 and CYP1A2, are also involved in pyridine metabolism, however, they only seem to play a

quantitatively significant role at high pyridine concentrations (Kim et al., 1991). Pyridine metabolites are mainly excreted in the urine, but may also be excreted in exhaled air and faeces (SCOEL, 2004). The nitrogen atom in pyridine may also undergo N-methylation, resulting in N-methyl pyridinium ion. However, the distribution of metabolites vary largely across both species and tissues. This was reviewed in the letter report from RIVM as follows and summarized in table 1:

"The overall fate of pyridine were examined by Damani et al. (1982), who administered [$_{14}$C]pyridine intraperitoneally to rats, mice, guinea-pigs, hamsters, gerbils, rabbits and cats, at a dose of 7 mg/kg bw. At least 50% of the administered ^{14}C was recovered in the urine of the animals. The amounts of the various specific metabolites differed markedly between the species. Only small amounts (0.4–5% of dose) of unchanged pyridine were found in most species, but cats and rabbits excreted 14% and 25% of the dose in the unchanged form. The extent of N-oxidation varied widely between species, from 0.3% of the dose applied in rats to 39% in hamsters. Pyridine N-oxide was not detected in rabbit urine. The excretion of N-methylpyridinium also varied between species, being lowest in gerbils (~2% of dose) and highest in cats (51% of dose). The major oxidation product was 4-pyridone (from 4% of the dose applied in hamsters to 19% in rabbits). 2-Pyridone and 3-hydroxypyridine were minor metabolites in all species, the former being absent from the metabolic profile in rabbits. Mice did not oxidize pyridine. The authors assumed that the occurrence of additional metabolic pathways is suggested by the excretion of unidentified products, accounting for up to 37% of the dose, in all species except guinea-pigs and cats. These pathways include glucuronidation of 3-hydroxypyridine, previously observed in rabbits." (Chen & Zijtveld, 2021)

Table 1. Species variations in the metabolic C- and N-oxidation and N-methylation of [14C]-labelled pyridine in various laboratory animals *in vivo*. From (Chen & Zijtveld, 2021).

	Total ^{14}C recovery (%)	% of dose in 0–24-h urine						
		Pyridine	N-Methyl pyridinium[a]	2-Pyridone	3-Hydroxypyridine	4-Pyridone	Pyridine N-oxide[b]	Unknown(s)
Rat	48	2	4(5)	1	2	10	0.5(0.3)	28
Mouse	66	2	21(12)	ND	ND	ND	5(6)	37
Guinea-pig	66	5	31(30)	2	2	18	9(8)	0
Hamster	67	0	17(26)	1	0.3	4	39(37)	6
Gerbil	52	0.4	1(2and3)	1	1	7	8(10)	34
Rabbit[c]	77	25	13(15)	0	4	19	0	17
Cat[d]	75	14	51(40)	2	1	10	3	0
Human	66	ND	(6 and 12)	ND	ND	ND	(32)	-25

Values obtained by high-performance liquid chromatography
ND, not determined
[a] Values in parentheses obtained by reverse isotope dilution
[b] Values in parentheses obtained by gas chromatography
[c] 0–72-h urine
[d] 0–48-h urine

Dose also impacts the metabolism of pyridine. N-methylation appears to be the preferred route of biotransformation at low doses, whereas at higher doses, such as 40 mg/kg bw, N-oxidation is more pronounced, varying from some 10% in rats to 20–40% in mice, hamsters, guinea-pigs, rabbits and ferrets (Damani et al., 1982). In concordance with this, the formation of N-methylpyridinium ion in rats fell from 10 to 0.8% (as a percentage of the administered dose) with increasing dose over the range 1–500 mg/kg bw (D'Souza et al., 1980). The administration route did not affect the result. However, the level of dose- dependency depends on species. In contrast to rats, guinea-pigs

excreted 31% of a dose as N-methylpyridinium independently of dose and unaffected by administration route.

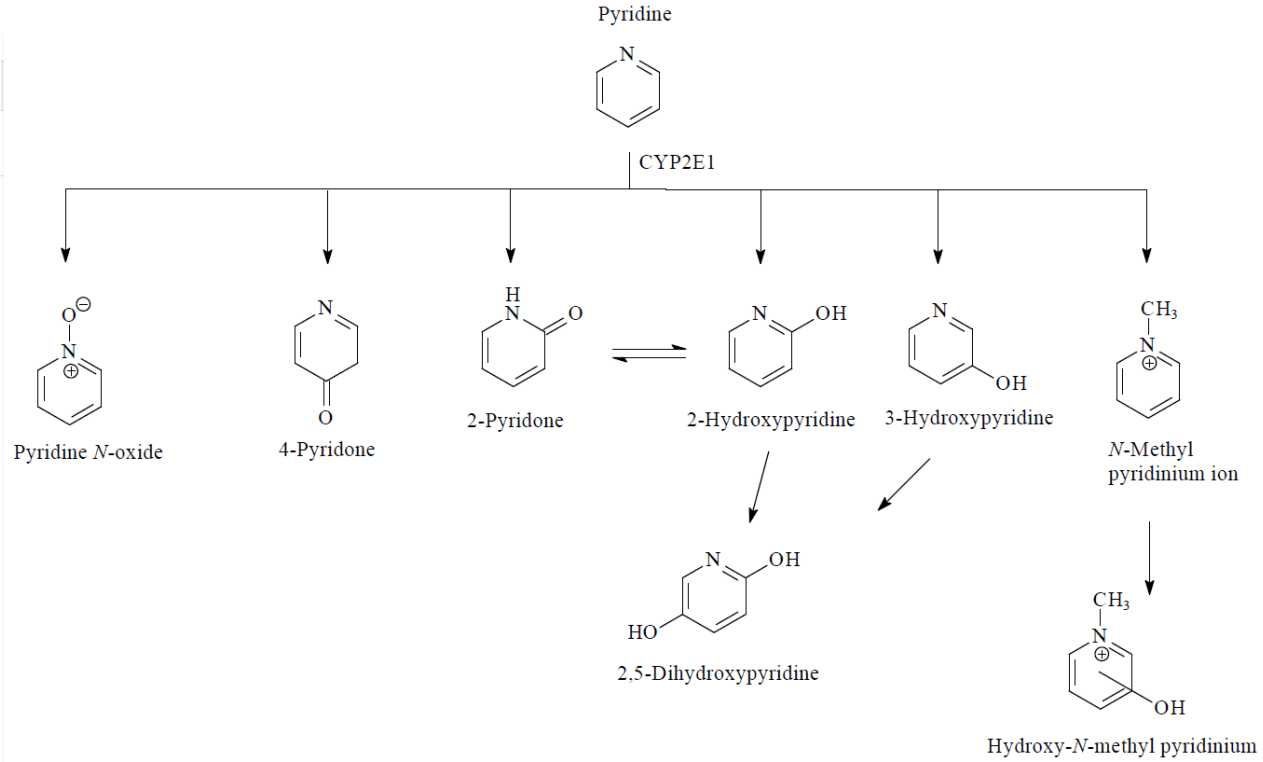


Figure 1. Illustration of identified metabolites of pyridine, most of which derive from the initial catalysis by cytochrome P450 2E1 (CYP2E1). The formation rate for each pyridine metabolite differs among tissues and species. Whereas most of the metabolites have been identified in all species studied, 2,5-dihydroxypyridine has only been characterized in rabbit liver microsomes. 2-Pyridone and 2-hydroxypyridine are in rapid equilibrium with each other. From (IARC, 2019a).

Human exposure
Monitoring
Airborne Pyridine

Methods of detection and quantification differ between media. For air monitoring, both NIOSH and OSHA have developed and issued methods of evaluating pyridine concentration (NIOSH, 1994; OSHA Salt Lake Technical Center, 1991). Both procedures analyse the samples by gas chromatography with flame ionization detection. The sample is collected in a sampling tube using a personal sampling pump. All procedures are described in detail in the abovementioned reports.

Biomonitoring

Some pyridine metabolites have been detected in humans after oral exposure. Two volunteers received 3.4 mg [14C]-pyridine in orange juice (approximately 0.05 mg/kg) and after 24 hours N-methylpyridinium ion (approx. 5.5% and 12% of the dose) was identified in urine (D'Souza et al., 1980). Pyridine-N-oxide was also detected, accounting for 32% of the administered dose (Damani et al., 1982)). Besides this small study, biomonitoring studies are very scarce in the literature. Therefore, no methods for biological monitoring of pyridine exposure were identified.

Exposure to Pyridine in the general population

The primary pyridine exposure routes are by ingestion, inhalation and dermal contact, both in occupational setting and for the general population. The major sources of pyridine exposure for the general population are food and tobacco smoke (Eatough et al., 1989; IARC, 2000; Maga, 1981)). Low concentration pyridine exposure may also occur by ingestion of pyridine-contaminated water (reviewed in (IARC, 2000)).

Pyridine has been identified in constituents of cigarette smoke (Eatough et al., 1989; Kulshreshtha & Moldoveanu, 2003; Saha et al., 2010; Wright, 2015). This was summarized by IARC as follows:

"Pyridine may be produced from nicotine degradation, and its quantity in mainstream cigarette smoke has been reported to range from 3 to 28 μg per cigarette. In 30 brands of cigarettes sold in China, the average pyridine yield was 17 μg per cigarette (standard deviation, 3.9 μg per cigarette). The yields measured by standard machine-smoking tests are misleading and have little value in the assessment of human exposure. Mean concentrations of pyridine in second-hand tobacco smoke in different studies ranged from 6.5 to 23.8 μg/m³. Pyridine was detected but not quantified in an electronic cigarette (e-cigarette). Analysis of e-cigarette solutions identified several pyridine derivatives, three of which were also identified in resultant aerosols." (IARC, 2019a)

Exposure through food may occur daily, as pyridine is a constituent in the volatile components of several foods produced by roasting and in canning processes. Pyridine was detected in corn tortilla chips at an approximate concentration of 30 μg/kg (Buttery & Ling, 1998), in fried bacon at 0.06 μg/kg (Timón et al., 2004), in mango fruit from non-

detectable amounts to 80 μg/kg (Pino et al., 2005), and in French press coffee at 4360 μg/kg and in Turkish coffee at 3904 μg/kg (Amanpour & Selli, 2016). In addition to this, pyridine has also been detected in fried chicken, French fries, roasted duck or goose, and tea (Baruth & Ternes, 2011; Ho et al., 2015; Jayasena et al., 2013). Total pyridine exposure has only rarely been estimated. In 1978, the EPA estimated a total pyridine intake in the US, mainly from food, of about 500 mg per year per person (EPA, 1978).

Occupational exposure levels

Exposure to pyridine may occur by inhalation and dermal contact during its production, or when used as an intermediate or as a solvent. Exposure may also occur in processes where pyridine is created as a waste product, e.g. in coke ovens, oil-shale plants, coffee processing facilities, sewage treatment plants, polymer combustion plants and other similar industries.

A wide range of pyridine occupational exposure levels have been reported. Three studies reported the highest levels around 20 mg/m^3. This was in a pyridine production area of a coal-tar plant in the Russian Federation, where pyridine levels were reportedly 7.5–10 mg/m^3 and occasionally reached 20 mg/m^3 (Izmerov, 1984). In a moulding area of a United States iron foundry, the 2-day average level of pyridine was 19 mg/m^3 (NIOSH, 1981). Lastly, pyridine air concentration in various workplaces in Poland during the second half of the 20th century ranged from 0.002 mg/m^3 to about 20 mg/m^3 (Sapota & Skrzypińska-Gawrysiak, 2013) as reported by (IARC, 2019a)). However, the majority of studies reported lower pyridine levels. Occupational exposure data for workplaces in the USA where pyridine was manufactured, used as a chemical intermediate, or used as a solvent in the 1970's were collected (IARC, 2000). Workers were exposed to 8-hour TWA pyridine concentrations ranging from 0.026 to 3.24 mg/m^3. A similar exposure level range was reported from coke works (0.005–2.98 mg/m^3) in Czechia, but with lower levels in blast furnaces, steel works, rolling mills, and foundries (≤ 0.63 mg/m^3) and in a Polish coke by-products plant (≤ 0.7 mg/m^3)(IARC, 2000). Low TWA pyridine concentrations of up to 0.29 mg/m^3 were also reported in research and development laboratories of a pyridine manufacturer (IARC, 2000), and an 8-hour TWA pyridine exposure of 0.3 mg/m^3 was estimated for a smell tester who used pyridine as one of their test substances (NIOSH, 1983). Similarly, pyridine levels from 22 measurements of workplace exposure in Finland in 2012–2016 ranged between 0.0006 and 0.5 mg/m^3 (FIOH, 2017).

Based on the presented data, the present working group notes occupational pyridine exposure levels ranging from not detectable and up to 20 mg/m^3. However large industry-, work process- and time-dependent differences were observed.

Cancer studies

Pyridine is classified as possible carcinogenic to humans (category 2B) by IARC in 2019 (IARC, 2019a). This is an upgrade from 2000, where pyridine was classified in category 3 (IARC, 2000), and this was based on increased evidence from animal studies. These will be covered in the animal studies chapter of the present report. Only one study investigating pyridine-induced cancer in humans was identified. In this study from 1991,

overall mortality and mortality from lung cancers were investigated in a cohort of 729 male workers from three plants manufacturing 4,4′-bipyridyl from pyridine in England (Paddle et al., 1991). The cohort included all employees working when the cohort was established in 1983 and all past employees in the manufacturing process since 1961. The authors assessed mortality up to the end of 1985 and as reference they used upscaled mortality rates from England and Wales to account for higher mortality rates in the area of manufacturing plants. Twenty-nine cancer deaths were observed versus 27.1 expected (SMR, 1.1 [95% CI, 0.7–1.5]). When the authors imposed a 10-year latency between the start of exposure and the start of follow-up, an excess of mortality from lung cancer was observed (SMR, 1.7 [95% CI, 0.9–3.1]), increasing to 2.1 after 15 years. The authors state that the increased lung cancer risk at 2.1 after 15 years was statistically significant at the 5% level, but did not provide 95% CI. Furthermore, data on the relationship between lung cancer and exposure to pyridine were not reported, and an examination of the exposure levels and time since exposure of the lung cancer cases did not support a causal interpretation. Therefore, albeit interesting, the study cannot be used for establishing an OEL for pyridine.

Other toxicological effects

As with cancer studies, human studies investigating other toxicological effects are very scares.

Acute toxicity

Acute pyridine toxicity in humans was briefly addressed in the report by the Scientific Committee on Occupational Exposure Limits (SCOEL) in their 2004 report:

"The acute lethal dose of pyridine for humans has been estimated to be 0.5 to 5.0 mg/kg. OSHA states that an air concentration of 3 600 ppm constitutes an immediate danger to life. A case of acute narcosis developed by a man after he had cleaned a tank that had contained pyridine has been reported. A 29-year-old man who accidentally swallowed half a cup of pyridine (approximately 125 ml) experienced nausea, dizziness, abdominal pain and lung congestion followed by death within two days."(SCOEL, 2004)

Irritancy

Similarly, SCOEL addressed pyridine irritancy in humans in the same report:

"In humans, pyridine is reported to be irritating to skin, eyes and mucous membranes. Pyridine in combination with light has damaged exposed skin. Pyridine has a sharp, unpleasant odour. The odour threshold for most individuals is around 0.2 ppm but perception can decrease with continued exposure. An air concentration of 10 ppm has been reported to be almost unbearable for an unaccustomed person. The threshold for irritation of nasal mucosa, i.e. effects on the trigeminus nerve, is about 700 ppm."(SCOEL, 2004)

Reproductive and developmental toxicity

(NTP, 2000)
No human studies on reproductive and developmental toxicity was identified by our literature search.

Animal studies

Since no epidemiological data is available on pyridine exposure and adverse outcomes, the present working group will focus on animal studies. The previously described literature search on pyridine exposure revealed a report from the National Toxicology Program (NTP) from 2000, which included three 13-week studies in mice (1 study) and rats (2 studies), and three cancer studies: one 2-year study in mice and two 2-year studies in rats (NTP, 2000). All studies were well-conducted good laboratory practice (GLP) studies that assessed both sexes. These studies investigated both cancerous changes and non-neoplastic changes following oral exposure. An overview of the studies is presented below. Additional animal experiments were identified in risk assessment reports by DECOS (DECOS, 1993) and SCOEL (SCOEL, 2004). These are described as well if considered relevant.

Short-term exposure (inhalation)

In a risk assessment report by SCOEL (SCOEL, 2004), an inhalation study in rats was identified (Nikula & Lewis, 1994). Rats were exposed by nose-only inhalation to 5 or 444 ppm of pyridine 6 hours per day for 4 days. This was associated with olfactory epithelial lesions in the nasal mucosa of male F344/N rats. The lesions were characterized by vacuolar degeneration of sustentacular cells, attenuation of the epithelium, loss of sensory neurons and intraepithelial luminal structures. Lesions were only slightly more severe in animals exposed to 444 ppm compared with rats exposed to 5 ppm (Nikula & Lewis 1994). SCOEL concludes that they are unable to identify a NOAEL and therefore unable to recommend an OEL. The current working notes that 16.2 mg/m^3 (5 ppm) was a LOAEL in the current study. Furthermore, the current working group notes that the 90-fold higher dose of 444 ppm only induced slightly more severe and this may indicate that a plateau has been reached already at 5 ppm.

Long-term exposure

Overview of the National Toxicology Program (NTP) 2 year studies

An on overview of the five two-year cancer studies is presented in Table 2 and further described in the text below.

Table 2. Summary of the NTP two-year studies (from NTP report).

	Male F344/N Rats	Female F344/N Rats	Male Wistar Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in drinking water	0, 100, 200, or 400 ppm	0, 100, 200, or 400 ppm	0, 100, 200, or 400 ppm	0, 250, 500, or 1,000 ppm	0, 125, 250, or 500 ppm
Body weights	200 and 400 ppm groups less than control group	200 and 400 ppm groups less than control group	Exposed groups less than control group	Exposed groups similar to control group	Exposed groups less than control group
Survival rates	25/50, 20/50, 25/50, 16/50	32/50, 37/50, 29/50, 26/50	22/50, 14/50, 11/50, 7/50	35/50, 28/50, 35/49, 35/50	32/50, 30/50, 22/50, 29/50
Nonneoplastic effects	Liver: centrilobular cytomegaly (0/50, 4/49, 8/50, 6/50); cytoplasmic vacuolization (4/50, 6/49, 13/50, 17/50); periportal fibrosis (0/50, 0/49, 2/50, 29/50); fibrosis (1/50, 1/49, 1/50, 10/50); centrilobular degeneration (1/50, 3/49, 2/50, 8/50); centrilobular necrosis (0/50, 3/49, 0/50, 5/50); pigmentation (4/50, 11/49, 20/50, 25/50)	Liver: centrilobular cytomegaly (0/50, 1/50, 4/50, 20/50); cytoplasmic vacuolization (10/50, 7/50, 9/50, 18/50); centrilobular degeneration (1/50, 2/50, 2/50, 7/50); bile duct hyperplasia (20/50, 29/50, 34/50, 29/50); pigmentation (6/50, 2/50, 6/50, 17/50)	Liver: centrilobular degeneration (1/50, 15/50, 25/50, 33/50); centrilobular necrosis (5/50, 6/50, 4/50, 23/50); fibrosis (1/50, 5/50, 26/50, 31/50); periportal fibrosis (0/50, 0/50, 5/50, 7/50); pigmentation (6/50, 15/50, 34/50, 42/50) Glandular Stomach: mineralization (8/49, 25/50, 16/48, 6/48) Parathyroid Gland: hyperplasia (16/48, 32/47, 29/48, 12/47)	None	None
Neoplastic effects	Kidney: renal tubule adenoma (standard evaluation - 1/50, 0/48, 2/50, 6/49; standard and extended evaluations combined- 2/50, 3/48, 6/50, 10/49); renal tubule adenoma or carcinoma (standard evaluation - 1/50, 1/48, 2/50, 6/49; standard and extended evaluations combined- 2/50, 4/48, 6/50, 10/49)	None	None	Liver: hepatocellular adenoma (29/50, 40/50, 34/49, 39/50); hepatocellular carcinoma (15/50, 35/50, 41/49, 40/50); hepatoblastoma (2/50, 18/50, 22/49, 15/50); hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (38/50, 47/50, 46/49, 47/50)	Liver: hepatocellular adenoma (37/49, 39/50, 43/50, 34/50); hepatocellular carcinoma (13/49, 23/50, 33/50, 41/50); hepatoblastoma (1/49, 2/50, 9/50, 16/50); hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (41/49, 42/50, 45/50, 44/50)
Uncertain findings	None	Mononuclear cell leukemia: (12/50, 16/50, 22/50, 23/50)	Testis: interstitial cell adenoma (5/50, 6/49, 4/49, 12/50)	None	None
Level of evidence of carcinogenic activity	Some evidence	Equivocal evidence	Equivocal evidence	Clear evidence	Clear evidence

Cancer

For all NTP studies on pyridine, rodents were exposed to pyridine in drinking water. The purity of pyridine was more than 99%.

Rats

2-year study in F344/N rats

Groups of 50 male and 50 female F344/N rats (7 weeks old) were exposed to pyridine in drinking water at concentrations of 0, 100, 200, or 400 ppm (equivalent to average daily doses of 7, 14, or 33 mg/kg) for 104 (males) or 105 (females) weeks.

Male rats

In Table 3, incidences of renal tubule tumours in male rats are presented as adenomas/carcinomas/combined adenomas and carcinomas and further if the evaluation was based on standard evaluation (single section) or extended evaluation (step sections) or combined standard and extended section. The incidence of adenomas was increased at the highest dose independent of the evaluation type with a significant dose-response trend, while there was no effect on incidence of carcinoma regardless of evaluation type. In the overall category that covers renal tubule adenoma or carcinoma (combined), standard (single section) and extended (step sections) evaluations combined, there was a statistically significant increase compared to controls at the highest dose (33 mg/kg bw/d) and there was a significant trend for the dose-response relationship.

Table 3. NTP study of carcinogenicity with pyridine in **male** F344/N rats (adapted from Table 3.1 from (IARC, 2019a))

Organ	**Tumor type**	**Tumor incidence**				**Statistical Significance**
Kidney		Dose (mg/kg bw/d)				
		0	7	14	33	
	Renal tubule adenoma, standard evaluation (single section)	1/50*	0/48	2/50	6/49**	*P=0.003 (trend) **P=0.042
	Renal tubule carcinoma, standard evaluation (single section)	0/50	1/48	0/50	0/49	NS
	Renal tubule adenoma or carcinoma (combined), standard evaluation (single section)	1/50*	1/48	2/50	6/49**	*P=0.008 (trend) **P=0.042
	Renal tubule adenoma, extended evaluation (step sections)	1/50*	3/48	5/50	9/49**	*P=0.031(trend) **P≤0.01
	Renal tubule adenoma, standard (single section) and extended (step sections) evaluations combined	2/50*	3/48	6/50	10/49**	*P=0.002 **P=0.008
	Renal tubule carcinoma, standard (single section) and extended (step sections) evaluations combined	0/50	1/48	0/50	0/49	NS
	Renal tubule adenoma or carcinoma (combined), standard (single section) and extended (step sections) evaluations combined	2/50*	4/48	6/50	10/49**	*P=0.003(trend) **P=0.008

NS: not significant

Female rats

In female rats, there was a significantly increased incidence of mononuclear cell leukaemia at the two highest doses (Table 4). However, due to a general high spontaneous background incidence of mononuclear cell leukemia in the F344 rat and species-specific biology, this tumor type is not regarded as appropriate relevant tumor type for human risk assessment (Maronpot et al., 2016) Therefore, the present working group does not consider the increased incidence of mononuclear cell leukaemia relevant for the human cancer risk assessment of pyridine.

Table 4. NTP study of carcinogenicity with pyridine in **female** F344/N rats (adapted from Table 3.1 from (IARC, 2019a))

Organ	**Tumor type**	**Tumor incidence**				**Significance**
All organs		Dose (mg/kg bw/d)				
		0	7	14	33	
	Mononuclear cell leukaemia	12/50*	16/50	22/50**	23/50***	*P=0.013 (trend) **P=0.043 ***P=0.020

2-year study in male Wistar rats

Groups of 50 male Wistar rats (7 weeks old) were exposed to pyridine in drinking water at concentrations of 0, 100, 200, or 400 ppm (equivalent to average daily doses of 8, 17, or 36 mg/kg) for 104 weeks. The incidence of testicular adenoma was significantly increased at the highest dose and there was a significant trend for the dose-response relationship (Table 5). However, compared to the controls, the survival of rats exposed to pyridine was halved or more at the two highest doses (Table 2. Summary of the NTP two year studies (from NTP report)(IARC, 2019a). The current working group, considers the increase in testicular adenoma at the highest dose as relevant, but the study unsuitable as basis for deriving health-based occupational exposure limits due to the low survival of rats exposed to pyridine.

Table 5. NTP study of carcinogenicity with pyridine in **male Wistar** rats (adapted from Table 3.1 from (IARC, 2019a))

Organ	**Tumor type**	**Tumor incidence**				**Significance**
Testis		Dose (mg/kg bw/d)				
		0	8	17	36	
	Testicular (interstitial cell) adenoma	5/50*	6/49	4/49	12/50**	*P=0.008 trend) **P=0.012

Mice

2-year study in mice

Groups of 50 male B6C3F1 mice were exposed to pyridine in drinking water at concentrations of 0, 250, 500, or 1,000 ppm (equivalent to average daily doses of 35, 65, or 110 mg/kg) for 104 weeks, and groups of 50 female B6C3F1 mice were exposed to pyridine in drinking water at concentrations of 0, 125, 250, or 500 ppm (equivalent to average daily doses of 15, 35, or 70 mg/kg) for 105 weeks. Survival of exposed mice (both female/male) was not different from controls.

Male mice

The incidences of hepatocellular adenoma, hepatocellular carcinoma and hepatoblastoma are shown in Table 6. The incidence of all tumor types are increased at the lowest dose (35 mg/kg bw/d) except for hepatoblastoma (multiple).

Table 6. NTP study of carcinogenicity with pyridine in **male** B6C3F$_1$ mice (adapted from Table 3.1 from (IARC, 2019a))

Organ	**Tumor type**	**Tumor incidence**				**Significance**
Liver		Dose (mg/kg bw/d)				
		0	35	65	110	
	Hepatocellular adenoma (multiple)	16/50*	29/50**	29/49**	28/50**	*P=0.018 (trend) **P≤0.05
	Hepatocellular adenoma (includes multiple)	29/50*	40/50*	34/49	39/50***	*P=0.031 (trend) **P=0.003 ***P=0.011
	Hepatocellular carcinoma (multiple)	3/50*	19/50**	26/49**	18/50**	*P<0.001 (trend) **P≤0.01
	Hepatocellular carcinoma (includes multiple)	15/50*	35/50**	41/49**	40/50**	*P<0.001 (trend) **P≤0.001
	Hepatoblastoma (multiple)	1/50	4/50	6/49*	2/50	*P≤0.05
	Hepatoblastoma (includes multiple)	2/50*	18/50**	22/49**	15/50**	*P=0.005 (trend) **P≤0.001
	Hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined)	38/50*	47/50**	46/49***	47/50****	*P<0.01 (trend) **P=0.002 ***P=0.003 ****P<0.001

Female mice

The incidences of hepatocellular adenoma, hepatocellular carcinoma and hepatoblastoma are shown in Table 7. The incidence of hepatocellular adenoma is high in the control mice (37 out of 49 mice have hepatocellular adenoma (includes multiple)). The incidence of hepatoblastoma (includes multiple) is increased at the two highest doses, while the incidence of hepatocellular carcinoma (includes multiple) is increased at the lowest dose (15 mg/kg bw/d).

The present working group considers that due to the high background incidence of hepatoadenoma in control mice, this tumor type is inappropriate for hazard assessment. Since hepatocellular carcinoma occurs at a lower dose than hepatoblastoma, hepatocellular carcinoma is considered as the critical endpoint for female mice and therefore considered relevant for the risk assessment.

Table 7. NTP study of carcinogenicity with pyridine in **female** B6C3F1 mice (adapted from Table 3.1 from (IARC, 2019a))

Organ	**Tumor type**	**Tumor incidence**				**Significance**
Liver		Dose (mg/kg bw/d)				
		0	15	35	70	
	Hepatocellular adenoma (multiple)	24/49	34/50*	37/50**	30/50	*P≤0.05 (trend) **P≤0.01
	Hepatocellular adenoma (includes multiple)	37/49	39/50	43/50*	34/50	*P=0.015
	Hepatocellular carcinoma (multiple)	3/49*	11/50**	14/50***	30/50***	*P<0.001 (trend) **P≤0.05 ***P≤0.01
	Hepatocellular carcinoma (includes multiple)	13/49*	23/50**	33/50***	41/50***	*P<0.001 (trend) **P≤0.014 ***P<0.001
	Hepatoblastoma (multiple)	0/49	0/50	3/50	4/50	NS
	Hepatoblastoma (includes multiple)	1/49*	2/50	9/50**	16/50***	*P<0.001 (trend) **P=0.007 ***P<0.001
	Hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined)	41/49*	42/50	45/50**	44/50***	*P=0.009 (trend) **P=0.042 ***P=0.045

Selection of critical cancer study

The present working group notes that cancer is observed in all animal studies. An overview of the five NTP studies with regard to critical effect, lowest cancer inducing dose and whether the studies can be used for risk assessment is presented in Table 8.

The present working group considers that the following studies can be used for risk assessment: the studies on male F344/N rats, female and male B6C3F1 mice. Among these, the present working group considers the female mouse study as the critical study with the lowest dose inducing cancer (15 mg/kg bw/d).

Table 8. Overview of the five NTP cancer studies and their relevance for risk assessment

NTP study	Critical effect	Lowest cancer inducing dose (mg/kg bw/d)	Suitable for risk assessment (comments)
Male Wistar rats	Testicular adenoma	36	NO (High mortality)
Female F344/N rats	Mononuclear cell leukaemia	33	NO (High spontaneously background)
Male F344/N rats	Renal tubule adenoma or carcinoma (combined)	33	YES
Female B6C3F1 mice	Hepatocellular carcinoma	15	YES
Male B6C3F$_1$ mice	Hepatocellular carcinoma	35	YES

Non-neoplastic effects

Inhalation

In a risk assessment report by DECOS, an inhalation study in rats was identified. Rats were exposed by inhalation to levels of either 10 or 50 ppm (32.3 or 161.5 mg/m^3) pyridine vapour, 5 days a week for 6 months. This resulted in increased liver weights (exposure levels with effect not specified)(Gehring, 1983)).

Oral

2 year NTP study

NTP summarized the non-neoplastic effects from the 2 year studies as follows: *"In F344/N rats, exposure to pyridine resulted in increased incidences of centrilobular cytomegaly and degeneration, cytoplasmic vacuolization, and pigmentation in the liver of males and females; periportal fibrosis, fibrosis, and centrilobular necrosis in the liver of males; and bile duct hyperplasia in females. In male Wistar rats, pyridine exposure resulted in increased incidences of centrilobular degeneration and necrosis, fibrosis, periportal fibrosis, and pigmentation in the liver, and secondary to kidney disease, mineralization in the glandular stomach and parathyroid gland hyperplasia"(NTP, 2000).*

An overview of the non-neoplastic lesions are presented in Table 2 (Summary of the NTP two year studies). Non-neoplastic findings, such as pigmentation, eosinophilic focus, centrilobular degeneration, and bile duct hyperplasia, were reported at the lowest dose (100 ppm) in both male and female F344/N rats and in male Wistar rats (NTP, 2000). However, as dose-response relationships are generally lacking, the present working group does not consider the dose of 100 ppm as the lowest-observed-adverse-effect level (LOAEL) for non-neoplastic lesions. Fibrosis and periportal fibrosis were observed in male Wistar rats at the dose of 17 mg/kg (200 ppm). As fibrosis was also observed for the high dose exposure in both male Wistar and F344/N rats, and due to the regulatory relevance of fibrosis, the present working group considers the dose of 200 ppm as the

LOAEL, and thereby the dose of 100 ppm (7 mg/kg) as the NOAEL for non-neoplastic lesions. Calculations will be based on this value.

13 week NTP study
F344/N rats (n=10 male and 10 female) were exposed to pyridine in drinking water equivalent to 5, 10, 25, 55, or 90 mg/kg bw/day (NTP, 2000).

Wistar rats (n=10 male) were exposed to pyridine in drinking water equivalent to 5, 10, 30, 60, or 100 mg/kg bw/day.

B6C3F1 mice (n=10 male and 10 female) were exposed to pyridine in drinking water equivalent to 10, 20, 50, 85, or 160 mg/kg bw/day for males and 10, 20, 60, 100, or 190 mg/kg bw/day for females.

NTP summarized the results from the 13-week drinking water studies as follows where rats and mice were exposed to 0 ppm, 50 ppm, 100 ppm, 250 ppm, 500 ppm and 1000 ppm: "*The target organs in the 13-week drinking water studies included the liver and kidney in male F344/N and Wistar rats and the liver in female F344/N rats. Decreased water consumption and/or body weight effects were observed in 1,000 ppm [190 mg/kg bw/day] mice in the 13-week study, but no target organ lesions were observed*"(NTP, 2000).

The present working group notes that the effects in the NTP 13- week study occurred at higher dose levels than the dose levels at which the critical effects are observed in the NTP cancer studies. Therefore, the results from the 13-week studies are not considered further in the present report and are not used in in relation to the risk assessment performed in chapter "Scientific basis for setting an occupational exposure limit".

Gavage
DECOS identified a gavage study, where rats were exposed to pyridine by gavage at doses of 0.25, 1.0, 10, 25 and 50 mg/kg for 90 days. Inflammatory hepatic lesions and increased absolute and relative liver weights were found at the highest dose administrated (RC, 1987). Increased relative liver weights were observed in female, but not in male rats, receiving 10 or 25 mg/kg pyridine.

Reproductive and developmental toxicity

NTP identified a study showing muscular hypoplasia in 15% or 67% of chicks following injection of 10 or 20 mg pyridine into eggs (NTP, 2000).

No additional studies were identified by our literature search.

An ECHA registration dossier describes a developmental toxicity study (OECD 421) that was undertaken on pyridine: "*Doses of 0, 12, 25 and 50 mg/kg bw/d were administered by oral gavage to male rats at doses for 2 weeks prior to mating, and to females for 2 weeks prior to mating and throughout the gestation and lactation periods. There were no adverse reproductive findings attributable to pyridine. Under the conditions of this study, a parental No Observed Effect Level (NOAEL) was not established due to the increased liver weights observed in all*

treatment groups. The NOEL for reproductive parameters was considered to be 25 mg/kg/day based on decreased mean numbers of live pups per litter on days 1 and 4 of lactation for the 50 mg/kg/day dose group. This study indicates that there is no adverse reproductive toxicity at doses several-fold higher than doses causing toxicity in the dams or adult males"(ECHA, 2008a).

The current working group is of the opinion that the identified studies on reproductive and developmental toxicity are not suitable for deriving an OEL.

Skin sensitisation

The literature search performed by the present working group did not identify any studies on sensitization.
ECHA concludes that "*conflicting data exist for the sensitisation potential of pyridine"* (ECHA, 2008b). This is based on the following: "*It [pyridine] is not sensitising in the guinea pig, while local lymph node data in the mouse suggests that it is a weak sensitiser. In the absence of firm data to the contrary, pyridine retains its harmonized classification of pyridine as a non-sensitiser (Regulation (EC) No. 1272/2008, Annex VI, Index # 613-002-00-7)*"(ECHA, 2008b).

The current working group is of the opinion that the identified studies are not suitable for deriving an OEL.

Mechanisms of toxicity

Cancer

Pyridine has been classified as possibly carcinogenic to humans (Group 2B) by IARC. However, a clear mechanism of action has not been established yet. IARC concludes that "*there is weak evidence that pyridine is genotoxic*" and "*moderate evidence that pyridine induces chronic inflammation*"(IARC, 2019a). Genotoxicity data for pyridine has been reviewed in previous reports (IARC, 2000, 2019a; NTP, 2000). This data will be summarized below. No human mutagenicity data were available.

Mutagenicity and genotoxicity

Mammalian systems

No micronuclei was detected in male ICR mice orally exposed to pyridine (Harper et al., 1984). Similarly, pyridine did not induce micronuclei or chromosomal aberrations in intraperitoneally injected male B6C3F1 mice (NTP, 2000). Unscheduled DNA synthesis was investigated in male B6C3F1 mice given pyridine by oral gavage at doses 175, 350, and 700 mg/kg body weight. The authors reported no evidence of unscheduled DNA synthesis in hepatocytes following exposure up to the maximum tolerated dose (MacGregor et al., 2000). However, some mildly adverse, reversible clinical signs were seen after exposure to the highest dose of pyridine.

Three studies reported no induction of chromosomal aberrations in Chinese hamster cells (both with and without rat liver S9) after exposure to pyridine (Abe & Sasaki, 1977; Ishidate & Odashima, 1977; NTP, 2000). Similarly, no significant increase in mutant frequencies were seen in L5178Y Tk+/− mouse lymphoma cell cultures after incubation with pyridine, both with or without rat liver S9 (McGregor et al., 1988). One study reported pyridine-induced increased levels of sister-chromatid exchange in Chinese hamster cells (without exogenous metabolic activation) (Abe & Sasaki, 1977), however such effect was not reported in another study with similar setup (NTP, 2000).

Non-mammalian systems

Genetic and related effects of pyridine in *D. melanogaster* has been investigated in several studies. These studies were summarized by IARC in 2019 as follows:

Pyridine yielded mixed results in experiments for induction of sex-linked recessive lethal (SLRL) mutations in adult male D. melanogaster. Valencia et al. (1985) reported negative results for pyridine administered by intraperitoneal injection (at 7000 ppm in aqueous 0.7% saline solution), whereas feeding (at 700 ppm pyridine in aqueous 5% sucrose) modestly increased recessive lethal mutations (P = 0.043). A second experiment using both intraperitoneal injection (at 500 ppm) and feeding (at 730 ppm) routes yielded negative results. In a third study, results of a feeding (at 500 ppm) experiment were negative, but administration of pyridine by intraperitoneal injection (at 4300 ppm) significantly increased the frequency of SLRL mutations. A follow-up test for induction of reciprocal translocations in germ cells of male D. melanogaster given pyridine produced negative results. Finally, increased frequencies of nondisjunction were observed in D. melanogaster broods arising from nearly mature oocytes, but not early-stage or mature oocytes,

after females were fed pyridine (at 0.05, 0.1, 0.2, and 0.3%) and mated to untreated males.(IARC, 2019a).

Pyridine has been tested in non-mammalian *in vitro* systems. Aneuploidy, possibly due to disruption of microtubule assembly, was reported in *Saccharomyces cerevisiae* D61.M after treatment with up to 1.09% pyridine (Zimmermann et al., 1986). However, no effect of pyridine was reported in bacterial reverse mutation assays in various *Salmonella typhimurium* strains, even at high doses (Florin et al., 1980; Haworth et al., 1983). Similarly, pyridine did not induce DNA strand breaks in ϕX-174 phage DNA after a single dose of 1 mM pyridine (Kim & Novak, 1990). Finally, no genetic or related effects of pyridine metabolites were found in most of the non-mammalian *in vitro* systems (Florin et al., 1980; Nagao & Sugimura, 1972; Voogd et al., 1980). However, the pyridine metabolite 2,5-Dihydroxypyridine induced dose-dependent increases in DNA strand breaks in ϕX-174 phage DNA (Kim & Novak, 1990).

Other mechanisms

IARC summarizes: "*Regarding the key characteristics of carcinogens, there is weak evidence that pyridine is genotoxic. No human data are available. Pyridine did not induce chromosome or DNA damage in mice. It gave positive results in a few tests in Drosophila melanogaster, and in a single test of sister-chromatid exchange induction in Chinese hamster cells in the absence of metabolic activation from S9. Pyridine did not induce mutations in bacterial test systems. There is weak evidence that pyridine induces oxidative stress. Two short-term studies in which pyridine was given by intraperitoneal injection, one in rats and one in hamsters, demonstrated oxidative stress. There is moderate evidence that pyridine induces chronic inflammation in rat liver from 13-week and chronic studies, in which necrosis and fibrosis were additionally shown. Renal tubule hyperplasia was observed in male rat kidney. In the chronic drinking-water study in male rats, toxic effects and carcinogenicity were seen in the kidney. Three of the seven criteria established by IARC for the induction of kidney tumours to have occurred by an α2u-globulin-associated response have not been met"(IARC, 2019a).*

Summary

The present working group concludes that there is limited positive data on genotoxicity and that there is no evidence for a clear mechanism of action for the carcinogenic effect of pyridine. This conclusion is aligned with IARC concluding that the evidence for genotoxicity of pyridine is weak. Furthermore, data from the Danish (Q)SAR Database show that pyridine is negative in domain in the Ames test for mutagenicity. In addition, the Database also reports that experimental data for Ames test are negative. Based on the above presented data, a non-threshold mechanism of carcinogenicity cannot be excluded, and in such cases, we choose a precautionary approach and recommend a linear extrapolation in the hazard assessment of carcinogenicity. This precautionary approach is based on ECHA REACH R8 (ECHA, 2012) in which it is stated that: "It is to be noted that the decision on a threshold and a non-threshold mode of action may not always be easy to make, especially when, although a biological threshold may be postulated, the data do not allow identification of it. If not clear, the assumption of a non-threshold mode of action would be the prudent choice. For mutagens/carcinogens, it

should be stressed that the Carcinogens and Mutagens Directive (2004/37/EC) requires that occupational exposures are avoided/minimised as far as technically feasible. As REACH does not overrule the Carcinogens and Mutagens Directive, the approach to controlling workplace exposure should therefore comply with this minimisation requirement." Consequently, the present working group decided to perform the hazard assessment based on a non-threshold mechanism of action for carcinogenesis. However, because the evidence for genotoxicity is weak, we choose also to include calculations for cancer as threshold effect for comparison.

PREVIOUS EVALUATIONS OF PYRIDINE

Occupational exposure limits

Several countries, regions and organizations have set occupational limits for pyridine exposure. These have been compiled in the GESTIS database (GESTIS, 2022) and are presented in table 9.

Table 9. Limit values for pyridine in different countries or regions.

	Limit value - Eight hours		Limit value - Short term	
Country or region	ppm	mg/m³	Ppm	mg/m³
Australia	5	16		
Austria	5	15	20	60
Belgium	1	3.3		
Canada - Ontario	1			
Canada - Québec	5	16		
Denmark	5	15	10	30
Finland	1	3	5 (a)	16 (a)
France	5	15	10	30
Hungary		15 (b)		30 (b)(a)
Ireland	5	15	10 (c)	30 (c)
Latvia	5	15		
New Zealand	1	3.2		
Norway	5	15		
People's Republic of China		4		
Poland		5 (b)		
Romania	5	15		
Singapore	5	16		
South Africa	2			
South Africa Mining	5	15	10 (a)	30 (a)
South Korea	2			
Spain	1	3		
Sweden	2	7	3 (a)	10 (a)
Switzerland	5	15	10	30
The Netherlands		0.9		
Turkey	5	15		
USA - NIOSH	5	15		
USA - OSHA	5	15		
United Kingdom	5	16	10	33

NIOSH: National Institute for Occupational Safety and Health. OSHA: Occupational Safety and Health Administration. Ppm: parts per million. (a) 15 minutes average value. (b) Skin. (c) 15 minutes reference period. Source: (IFA, 2024)(assessed November 9th, 2022).

Previous reports

As no suitable human studies or inhalation studies on pyridine exposure exist in the literature, previous reports have derived OELs based on oral exposure in animal models.

Dutch Expert Committee on Occupational Safety (DECOS), 1993

In 1993, the Dutch Expert Committee on Occupational Safety (DECOS) and the Swedish Criteria Group for Occupational Standards (SCG) collaborated on a joint scientific criteria document, aimed at being used by the national regulatory authorities in both the Netherlands and Sweden (DECOS, 1993). In this report, a brief overview of pyridine monitoring and previous evaluations was presented, followed by an evaluation of human risk.

The short-term occupational exposure limit was based on a study reporting symptoms of headache, nervousness, sleeplessness and occasional digestive tract problems at levels of 19.4 to 42 mg/m^3 (6 - 13 ppm) pyridine in workroom air (Ellenhorn & Barceloux, 1988). From these events, the authors concluded that the short-term occupational exposure limit should be below 19.4 mg/m^3.

Although the authors identified one human long-term exposure study, the data could not be used for hazard assessment because the doses were too high and the participants were epileptic patients who used pyridine as drug for anticonvulsant treatment (Pollock et al, 1943 (as referred by (DECOS, 1993)). The authors also decided that data on the carcinogenic potential of pyridine were inadequate to be of use in the hazard assessment. Instead, the authors identified two animal experiments important for hazard assessment. In the first study, rats were exposed by inhalation to levels of either 10 or 50 ppm (32.3 or 161.5 mg/m^3) pyridine vapour, 5 days a week for 6 months. This resulted in increased liver weights (not specified at which exposure levels the effect occurred) (Gehring, 1983). In the other study, rats were exposed to pyridine by gavage at doses of 0.25, 1.0, 10, 25 and 50 mg/kg for 90 days. Inflammatory hepatic lesions and increased absolute and relative liver weights were found at the highest dose administrated (RC, 1987). Increased relative liver weights were observed in female, but not in male rats, receiving 10 or 25 mg/kg pyridine. Based on this study, the authors of the report from DECOS concluded that the NOAEL for liver weight was 1 mg/kg b.w. per day. This was extrapolated from rat to man resulting in a NOAEL of 7 mg/m^3 (2 ppm), when considering a human weight of 70 kg and a breathing of 10 m^3 volume of air in 8 hour. This extrapolation is based on the assumption that 100% of the pyridine is absorbed through the digestive tract as well as respiratory tract, since the compound is completely soluble in water and penetrates very well through the skin.

The model proposed by DECOS contain some uncertainties and several assumptions are made, e.g. the use of gavage as a method of administration, which is not the assumed normal exposure route, and the 100% absorption through the respiratory tract. DECOS therefore proposed to use a safety factor of 10 and an upward round off, which lead to a health-based recommended occupational exposure limit of 1 mg/m^3 (0.3 ppm) TWA 8 hour for pyridine vapour with a skin notation.

Scientific Committee on Occupational Exposure Limits (SCOEL), 2004

SCOEL concludes as follows: "*The critical effect after short-term exposure is irritation of the mucous membranes of the upper respiratory tract and eyes, together with acute effects on the central nervous system. The critical identified long-term effects in experimental animals are on the liver and kidney; however, little work has been done on the potential long-term effects of inhaled pyridine, particularly on the respiratory tract. The NTP 2-year studies in rats and mice have indicated that pyridine has a carcinogenic effect in mice and rats (NTP 2000). However, it appears that pyridine is not genotoxic. The mechanisms by which the rodent tumours were produced have not been fully elucidated, but it is likely that they were non-genotoxic in nature. Their relevance to human health is doubtful; even if relevant, they would not occur if exposures were maintained below the levels at which precursor toxic effects occur. From the data available, SCOEL concluded that it is not possible to derive a health-based limit value for pyridine. An exposure level of 5 ppm produced lesions in the nasal olfactory epithelium of rats after only 4 days (6 hours per day), with no NOAEL having been identified. The most likely explanation for this finding is that it is the result of metabolic activation of pyridine at this site. There is uncertainty about what the consequences would be in the rat nasal epithelium of repeated exposure for a much longer period. There is also uncertainty about the extrapolation of any such findings in the rat to predictions of consequences for human health. Nevertheless, the rat nasal lesions are of major concern, so that SCOEL felt that is not possible to identify with confidence a level of inhalation exposure that does not pose a concern of toxicity to the upper respiratory tract in humans. These considerations, and early reports of adverse health effects in humans exposed to airborne concentrations reportedly in the range 6-13 ppm, led SCOEL to recommend that occupational exposures to pyridine should be maintained well below 5 ppm. As pyridine can be absorbed through the skin and consequently, could pose a threat of systemic toxicity, a "Sk" notation is justified*"(SCOEL, 2004).

IARC, 2019

IARC concludes as follows:

"5.*1 Exposure data*

Pyridine has several applications in organic chemistry and in industrial practice. It is a high production volume chemical. Pyridine can be formed from the breakdown of many natural materials in the environment. Due to its variety of applications, pyridine can be released in air, water, and soil. The major sources of exposure to pyridine for the general population are foods and cigarette smoke. Information about pyridine content in specific foods is scarce, but was quantified in the volatile components of coffee and in fried or roasted food. The estimated pyridine intake in the USA was less than 1 g/year per person. Occupational exposure may occur by inhalation and dermal contact during the production or use of pyridine as an intermediate or as a solvent. Exposure can also occur at coke ovens, oil-shale plants, and other similar industries. People working in quality control and research laboratories can also be exposed to pyridine.

5.2 Human carcinogenicity data

One small cohort study of mortality in workers exposed to pyridine and numerous other chemicals did not show any excess of mortality from cancer of the lung or all cancers combined. Six cases of squamous cell carcinoma of the skin were observed in the study population, but no risk data were reported.

5.3 Animal carcinogenicity data

In one well-conducted good laboratory practice (GLP) study in male and female mice given drinking-water containing pyridine, there was a significant increase, with a significant positive trend, in the incidence of hepatocellular adenoma, hepatocellular carcinoma, hepatoblastoma, and the combination of these tumours in males and females. In another well-conducted GLP drinking-water study in male and female F344/N rats, pyridine significantly increased the incidence of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) in males, and of mononuclear cell leukaemia in females, with a significant positive trend. In a third well-conducted GLP drinking-water study in male Wistar rats, pyridine significantly increased the incidence of testicular cell adenoma with a significant positive trend. One study in male and female rats given pyridine by subcutaneous injection gave negative results. One feeding study and one skin-application study in transgenic mice gave negative results.

5.4 Mechanistic and other relevant data

Few data on absorption, distribution, metabolism, or excretion of pyridine in humans were available. Pyridine is absorbed following oral exposure in humans and other species, as well as by other routes in experimental animals. Pyridine N-oxide is the primary metabolite in humans and other species, and is generated through cytochrome P4502 E1-mediated oxidation. Pyridine induces multiple cytochrome P450s, and affects the metabolism and toxicity of other chemicals, such as carbon tetrachloride. Regarding the key characteristics of carcinogens, there is weak evidence that pyridine is genotoxic. No human data are available. Pyridine did not induce chromosome or DNA damage in mice. It gave positive results in a few tests in Drosophila melanogaster, and in a single test of sister-chromatid exchange induction in Chinese hamster cells in the absence of metabolic activation from S9. Pyridine did not induce mutations in bacterial test systems. There is weak evidence that pyridine induces oxidative stress. Two short-term studies in which pyridine was given by intraperitoneal injection, one in rats and one in hamsters, demonstrated oxidative stress. There is moderate evidence that pyridine induces chronic inflammation in rat liver from 13-week and chronic studies, in which necrosis and fibrosis were additionally shown. Renal tubule hyperplasia was observed in male rat kidney. In the chronic drinking-water study in male rats, toxic effects and carcinogenicity were seen in the kidney. Three of the seven criteria established by IARC for the induction of kidney tumours to have occurred by an α2u-globulin-associated response have not been met.

6. Evaluation 6.1 Cancer in humans

There is inadequate evidence in humans for the carcinogenicity of pyridine.

6.2 Cancer in experimental animals

There is sufficient evidence in experimental animals for the carcinogenicity of pyridine.

6.3 Overall evaluation Pyridine is possibly carcinogenic to humans (Group 2B)"(IARC, 2019a).

National Institute for Public Health and the Environment (RIVM letter report), 2021

The aim of the report is "*to identify and summarize the available data from studies with laboratory models, test animals and humans on the substance pyridine. The focus of the current literature review will be on the mutagenic and carcinogenic properties of this substance. At the request of the Dutch Minister of Social Affairs and Employment, the Health Council of the Netherlands will use the summaries to assess the mutagenic and carcinogenic properties and to provide a recommendation for its classification. The assessment will be performed by the Health Council's Subcommittee on Classifying Carcinogenic Substances. This subcommittee falls under the Dutch Expert Committee on Occupational Safety, which focuses on health risks associated with occupational exposure of workers to chemicals. The current RIVM-report does not include an assessment of the reported mutagenic and carcinogenic effects of pyridine, nor does it include a conclusion regarding classification of the substance based on the CLPcriteria*"(Chen & Zijtveld, 2021).

Scientific basis for setting an occupational exposure limit

As mentioned previously, human toxicological data are very scarce and not suitable for deriving an OEL. All calculations are therefore made on data from animal experiments. Based on the available evidence the current working group considers pyridine-induced cancer and hepatic fibrosis as critical effects. Two inhalation studies were identified. However, the exposure levels and the associated LOAEL was much higher than in the oral study. Thus, although the main occupational route for pyridine is inhalation and dermal exposure, the present working group considers the oral studies more suitable for deriving exposure limits. In this report, the current working group will therefore calculate proposed occupational exposure limits based on the large oral study in mice and rats by NTP (NTP, 2000). This will be both DNELs based on threshold effects (fibrosis) and OELs based on non-threshold effects (cancer).

Calculations of exposure limits based on cancer as non-threshold effect and threshold effect

Pyridine is classified as possibly carcinogenic to humans (Group 2B). As summarized in the mechanism of toxicity section, there is weak evidence that pyridine is genotoxic (and no clear mode of action for pyridine-induced cancer exists). Since a non-threshold mechanism-of-action for pyridine-induced cancer cannot be excluded, the present working group considers pyridine-induced cancer in mice as non-threshold mechanisms. Calculations are based on an approach suggested by ECHA (ECHA, 2012b), using data on cancer reported in the two year oral study in mice (NTP, 2000). A high background level of hepatocellular adenomas were observed among both male and female mice in this study. This endpoint will therefore not be used for calculations. The lowest reported cancer-inducing pyridine dose was 15 mg/kg b.w. per day (125 ppm) in female mice, which caused hepatocellular carcinomas. Because of the weak evidence for genotoxicity of pyridine, the present working group has decided to perform calculations based on this exposure level for both cancer as a non-threshold and a threshold effect.

Observed excess cancer incidence at 15 mg/kg b.w. per day (125 ppm) in female mice:

(Incidence 125 ppm (female) – Incidence control (female)) / (1-(Incidence control (female))) =

(23/50 – 13/49)/(1-(13/49)) = 0.265 or 26.5%

For the conversion of dose metric into a human inhalation dose situation, the current working group uses following assumptions:

100% pyridine absorption through the digestive tract and the lung (Reinhardt & Brittelli, 1981) and (Santodonato, 1985) as referred by (DECOS, 1993).

An average human weight 70 kg.
The standard value of human ventilation is 20 L/min during light work (1.2 m^3/h), which sums up to 10 m^3 in an 8 hour work day.

The oral dose for the mouse is converted to the corresponding air concentration for humans using the method presented by ECHA, Chapter R.8, Example R. 8-2 workers (page 59):

First, the oral LOAEL is transferred to humans with a factor of 7 for allometric scaling (according to Table R. 8-3 and example R.8-2 , page 24, ECHA, chapter 8):

15 mg/kg/day / 7 = 2.143 mg/kg/day

Secondly, the dose is transferred to air concentration using a standard human body weight (70 kg) and default human breathing volume for workers during an 8 hour work with light activity (10 m^3):

2.143 mg/kg/day * 70 kg / 10 m^3 = 15 mg/m^3 = 15 000 μg/m^3

Cancer as a non-threshold effect

This is used as the starting point for the inhalation unit risk, which is an estimate of the increased cancer risk from inhalation exposure to a concentration of 1 μg/m^3 pyridine for a work life.

Calculation of unit risk for cancer:

Risk level = exposure level x unit risk
0.265 = 15,000 μg/m^3 x unit risk
Unit risk = 0.1767 x 10^{-4} per μg/m^3

Calculation of dose levels corresponding to risk level of 10^{-5} (and other risk levels)

10^{-5} risk level = exposure level x unit risk (0.1767 x 10^{-4} per μg/m^3)
Exposure level (10^{-5}) = 0.566 μg/m^3 = 0.000566 mg/m^3

Table 10. Calculated excess lung cancer incidence at different pyridine air concentrations.

Excess lung cancer incidence	Pyridine air concentration (mg/m^3)	Pyridine air concentration ($\mu g/m^3$)
1:1,000	0.0566	57
1: 10,000	0.00566	5.7
1: 100,000	0.000566	0.57

Cancer as a threshold effect

The corrected LOAEL of 15 mg/m^3 is adjusted by a number of assessment factors (of which most are default values suggested by ECHA).

The following default assessment factors are therefore used:
Interspecies extrapolation: 2.5
Intraspecies interpolation (default factor for workers): 5
LOAEL to NOAEL: 10
Severity of effect: 3 (liver carcinoma)

The overall assessment factor:

$AF_{overall\ min} = 2.5 * 5 * 10 * 3 = 12.5 = 375$

$DNEL_{min} = NOAEL_{corr}/AF_{overall\ min}$ = 15 mg pyridine/m^3 / 375 = 0.04 mg/m^3 = 40 $\mu g/m^3$

Calculations of exposure limits based on non-neoplastic hepatic changes and olfactory mucosal lesions as threshold effect

Non-neoplastic hepatic changes

The present working group considers pyridine-induced hepatic changes in rats as threshold effects. DNELs will be calculated as recommended by ECHA for toxicological effects having thresholds (ECHA, 2012a, b), and will be based on the findings reported in the 2 year rat study from the National Toxicology Program (NTP, 2000). Non-neoplastic findings, such as pigmentation, eosinophilic focus, centrilobular degeneration, and bile duct hyperplasia, were reported at the lowest dose (100 ppm) in both male and female

F344/N rats and in male Wistar rats (NTP, 2000). However, as dose-response relationships are generally lacking, the present working group does not consider the dose of 100 ppm as the lowest-observed-adverse-effect level (LOAEL). Fibrosis and periportal fibrosis were observed in male Wistar rats at the dose of 17 mg/kg (200 ppm). As fibrosis was also observed for the high dose exposure in both male Wistar and F344/N rats, and due to the regulatory relevance of fibrosis, the present working group consider the dose of 200 ppm as the LOAEL, and thereby the dose of 100 ppm (7 mg/kg) as the NOAEL. Calculations will be based on this value.

Calculations
First the NOAEL is corrected to fit a human inhalation dose situation. The following assumptions are used:

100% pyridine absorption through the digestive tract and the lung.
An average human weight 70 kg.
The standard value of human ventilation is 20 L/min during light work (1.2 m^3/h), which sums up to 10 m^3 in an 8 hour work day.
Allometric scaling (from rat to human): 4 (ECHA, chapter 4, Table R. 8-3, page 24)

Corrected NOAEL:
7 mg/kg/day * 70 kg / 10 m^3 /4 = 12.25 mg pyridine/m^3.

Secondly, the corrected NOAEL is adjusted by a number of assessment factors (of which most are default values suggested by ECHA).

The following default assessment factors are therefore used (ECHA, 2012b):

Interspecies extrapolation: 2.5
Intraspecies interpolation (default factor for workers): 5

The overall assessment factor, $AF_{overall\ min}$ = 2.5 * 5 = 12.5

This results in a DNEL for chronic inhalation for hepatic fibrosis:
$DNEL_{min}$ = $NOAEL_{corr}/AF_{overall\ min}$ = 12.25 mg pyridine/m^3 / 12.5 = 0.98 mg/m^3 =980 μg/m^3

Olfactory mucosal lesions following acute exposure

The present working group considers pyridine-induced olfactory mucosal lesions in rats as threshold effects. DNELs will be calculated as recommended by ECHA for toxicological effects having thresholds (ECHA, 2012a, b), and will be based on the findings reported in a rat study where rats following nose-only inhalation 6 h/day for 4 days to 16.2 mg/m^3 (5 ppm) pyridine developed olfactory mucosal lesions.

Calculations

First the LOAEL is corrected to fit a human inhalation dose situation. The following assumptions are used:

100% pyridine absorption through the digestive tract and the lung.
The standard value of human ventilation is 20 L/min during light work (1.2 m^3/h), which sums up to 10 m^3 in an 8 hour work day.

Corrected LOAEL:
16.2 mg/m^3 * 6 h/8h * 6.7 m^3/ 10 m^3 = 8.14 mg pyridine/m^3.

Secondly, the corrected LOAEL is adjusted by a number of assessment factors (of which most are default values suggested by ECHA).
The following default assessment factors from ECHA are used (ECHA, 2012b):

Interspecies extrapolation: 2.5
Intraspecies interpolation (default factor for workers): 5
LOAEL to NOAEL: 10 (the default factor of 10 was chosen since there were very poor dose response relationship between the two dose levels of 5 and 444 ppm)
Duration of exposure: 6

The ECHA default assessment factor from subacute (28 days of exposure) to chronic exposure is 6. The present working group notes that since correction from 4 days of exposure is needed a default factor of 6 is in the low end.

The overall assessment factor, $AF_{overall\ min}$ = 2.5 * 5 * 10 * 6= 750

DNEL = 8.14 mg/m^3/750 = 0.0109 mg/m^3 = 11 μg/m^3

Overview of calculated DNELs and risk levels

Table 11 shows an overview of the DNELs and risk levels calculated for threshold and non-threshold-effects, respectively. As described in the chapter on mechanisms there is weak evidence for the genotoxicity of pyridine. Since a non-threshold mechanism-of-action for pyridine-induced cancer cannot be excluded, the present working group considers pyridine-induced cancer in mice as non-threshold mechanism. However, because of the weak evidence for pyridines genotoxicity, the present working group has also chosen to present calculations if cancer is considered a threshold effect for comparison. When considered a threshold effect the calculated DNEL for cancer is 40 μg/m^3. This equals approximately an excess of cancer incidences between 1:1,000 at 57 μg/m^3 and 1:10,000 at 5.7 μg/m^3 when cancer is considered a non-threshold effect. Based on acute effects in the nose a threshold effect was derived at 11 μg/m^3. This threshold

limit is similar to the dose level corresponding to excess liver cancer risk of 1:10,000 at 5.7 μg/m^3 when cancer is considered a non-threshold effect.

Table 11. Overview of calculated DNEL's for threshold effects (hepatic and mucosal changes and cancer) and risk levels for cancer as non-threshold effect.

Threshold effects			DNEL
	Short-term	Olfactory mucosal lesions	11 μg/m^3
	Long-term	Non-neoplastic hepatic changes	980 μg/m^3
	Long-term	Cancer	40 μg/m^3
Non-threshold effects			Risk levels
	Long-term	Cancer	1: 1000 at 57 μg/m^3
			1:10,000 at 5.7 μg/m^3
			1:100,000 at 0.57 μg/m^3

Skin notation

The current working group recommends a skin notation for pyridine due to its rapid absorption through intact skin and its water and lipid solubility (Reinhardt & Brittelli, 1981) and (Santodonato, 1985) as referred by (DECOS, 1993).

This is in line with previous recommendations by SCOEL(SCOEL, 2004) and DECOS (DECOS, 1993):
SCOEL concludes*: "As pyridine can be absorbed through the skin and consequently, could pose a threat of systemic toxicity, a "Sk" notation is justified.""*

DECOS, 1993: "*It [pyridine] is also rapidly absorbed through intact skin[(Reinhardt & Brittelli, 1981)]. Based on its aqueous and lipid solubility, the absorption of pyridine is expected to be rapid [(Santodonato, 1985)]*".

Conclusion

The current working group considers pyridine-induced cancer and lesions in the nose as critical effects. The current working group has calculated health-based OELs based on cancer data from 2 year oral animal studies from the National Toxicology Program (NTP, 2000) and in addition for lesions in the nose based on a 4-day inhalation study in rats (Nikula & Lewis, 1994).

Since a non-threshold mechanism-of-action for pyridine-induced cancer cannot be excluded, the present working group considers pyridine-induced cancer in mice as non-threshold mechanisms. Calculations were based on data on cancer reported in the oral two-year study in mice (NTP, 2000). The expected excess lung cancer risk based on these data is 1: 1 000 at 57 μg/m^3, 1: 10 000 at 5.7 μg/m^3 and 1: 100 000 at 0.57 μg/m^3. The current working group notes that the health based OEL based on cancer as a threshold effect at 40 μg/m^3 which is similar to the risk estimate at 1:1000.

The present working group considers pyridine-induced nose lesions in rats as a threshold effect. DNEL is based on the findings reported in the 4-day rat study. This results in a DNEL at 11 μg/m^3 for olfactory mucosal lesions.

The present working group notes that the study on changes in the nose mucosa is based on a study with inhalation which is the occupationally relevant exposure route while the cancer risk estimates are based on an oral mouse study. This means that the risk estimates based on the cancer study come with additional uncertainties due to 1) the use of a different exposure route than what is relevant in an occupational setting, and 2) an unclear mechanism-of-action for genotoxic effect.

On that background the present working group is of the opinion that both risk estimates should be taken into account. These are listed in the table below:

Table 12. Overview of final risk estimates

Threshold effects	Study type	Critical effect	DNEL
	Short-term animal study	Olfactory mucosal lesions	11 μg/m^3
Non-threshold effects			Risk levels
	Long-term animal study	Cancer	1: 1000 at 57 μg/m^3
			1:10,000 at 5.7 μg/m^3
			1:100,000 at 0.57 μg/m^3

Finally, the current working group recommends a skin notation for pyridine due to its rapid absorption through intact skin and its water and lipid solubility (Reinhardt & Brittelli, 1981) and (Santodonato, 1985) as referred by (DECOS, 1993).

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Appendix 1. Litterature search

PubMed

An up-to-date (August 2022) search on PubMed using the same search terms as RIVM, 2021 resulted in 11 published papers (Chen & Zijtveld, 2021). A second search was performed to identify studies focusing on inflammation, acute phase response, cardiovascular disease and reproductive toxicity. Table 13 presents the search terms and the results for the database PubMed.

Table 13. Search strategy and results for PubMed.

Query	Search terms	Number of records
#1	"pyridine"[Supplementary Concept] OR "Pyridines/toxicity"[MAJR:NoExp] AND "pyridin*"[tw]	3,682
#2	"Inflammation"[Mesh] OR "atherosclerosis"[Mesh]	441,416
#3	"acute phase response*"[tw] OR "cardiovascular*"[tw] OR "inflammation*"[tw] OR "male reproduction*"[tw] OR "female reproduction*"[tw] OR "developmental tox*"[tw] OR "reprotox*"[tw] OR "reproductive tox*"[tw] OR “fertility”[tw] OR “semen”[tw] OR “oocyte”[tw]	1,456,817
#4	#2 OR #3	1,669,210
#5	#1 AND #4	92

The search resulted in 92 identified records. Combined with the up-to-date search, a total of 103 unique published papers were identified in Pubmed. These were then subjected to a title and abstract read-through to identify articles relevant to pyridine exposure. This resulted in 2 articles for full review.

Web of Science

The Web of Science database was not utilized in the RIVM report (Chen & Zijtveld, 2021) and a completely new search was conducted. Table 14 present the search terms and the results for the database Web of Science. The search was performed from 1993 and onwards to cover literature published since DECOS published their risk assessment of pyridine (DECOS, 1993)

Table 14. Search strategy and results for Web of Science.

Query	Search terms	Number of records
#1	TS= "pyridine"	102,335
#2	WC="Toxicology"	470,213
#3	TS="Toxicokinetics" OR TS="Carcinogenesis" OR TS= "Mutagenesis" OR TI= "toxic*" OR TI="carcinogen*" OR TI="mutagen*" OR TI="mutat*" OR TI="genotox*" OR TS="epigen*" OR TI="genetic*" OR TS="micronucle*" OR TS="transgen*"	1,555,517
#4	#2 OR #3	1,933,809
#5	#1 AND #4	2,276
#6	TS="exposure monitor*" AND (TS="environment*" OR TS="human") OR TS="biologic*"	1,385,595
#7	TS="metabolism" OR TS="adme" OR TS="absorption-distribution-metabolism-excretion"	947,295
#8	#6 OR #7	2,271,255
#9	#1 AND #8	6,978
#10	#1 AND #8 and (1994 or 1993 or 1995 or 1996 or 1997 or 1998 or 2022 or 2021 or 2020 or 2019 or 2018 or 2017 or 2016 or 2015 or 2014 or 2013 or 2012 or 2011 or 2010 or 2009 or 2008 or 2007 or 2006 or 2005 or 2004 or 2003 or 2002 or 2001 or 2000 or 1999) (Publication Years)	6,595
#11	TS="atherosclerosis" OR TS="acute phase response" OR TS="cardiovascular*" OR TS="inflam*" OR TS= "male reproduction" OR TS="female reproduction" OR TS="developmental tox*"[tw] OR TS="reprotox*" OR TS="reproductive tox*" OR TS=fertility OR TS=semen OR TS=oocyte	2,216,195
#12	#1 AND #11	1,098
#13	#10 OR #12	7,402
#14	#13 AND English (Languages) AND Meeting Abstract (Exclude – Document Types)	7,220
#15	#10 OR #12 and Meeting Abstract (Exclude – Document Types) and English (Languages) and Toxicology or Oncology or Cell Biology or Immunology or Cardiac Cardiovascular Systems or Respiratory System or Reproductive Biology or Dermatology or Urology Nephrology or Developmental Biology or Biology (Web of Science Categories)	688

The search in Web of Science resulted in 688 records, which were then subjected to a title and abstract read-through to identify articles relevant to pyridine exposure. This resulted in 26 records for full review.

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