DIMETHYLFORMAMIDE

CAS number: 68-12-2

Synonyms: DMF, N,N-Dimethylformamide, formyldimethylamine, formamide

Chemical formula: C_3H_7NO

Workplace exposure standard (amended)

TWA: **5 ppm (15 mg/m^3)**

STEL: **—**

Peak limitation: **—**

Notations: **Sk.**

IDLH: **500 ppm**

Sampling and analysis: The recommended value is quantifiable through available sampling and analysis techniques.

Recommendation and basis for workplace exposure standard

A TWA of 5 ppm (15 mg/m^3) is recommended to protect for adverse effects in the liver and irritation of the eyes and upper respiratory tract in exposed workers.

Discussion and conclusions

Dimethylformamide (DMF) is widely used as a solvent in the production and processing of polymers and pharmaceuticals, as a co-solvent in the manufacture of protective coatings, adhesive, printing inks, fibres and synthetic leather, and as a catalyst and carrier for gases in various industrial processes (ACGIH, 2018; HCOTN, 2011; US EPA, 1990).

The critical effects are irritation of the eyes and upper respiratory tract and systemic toxicity including liver injury. Epidemiological studies in workers suggest systemic toxicity including liver injury after dermal absorption, with potential liver enzyme changes and alcohol intolerance reported at less than 10 ppm (ACGIH, 2018). Abnormal liver function was not observed in plant workers with long-term exposures at 5 ppm. A two year inhalation study in rats and mice reported a NOAEC (rats) and LOAEC (mice) of 25 ppm for liver effects (ACGIH, 2018). A NOAEC of 31 ppm is identified in rats for developmental effects (DFG, 2017).

A TWA of 5 ppm adopted from ACGIH (2018) and DFG (2016) is recommended. This TWA is protective of irritation effects, adverse liver effects and possible developmental effects.

Recommendation for notations

Not classified as a carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Not classified as a skin sensitiser or respiratory sensitiser according to the GHS.

A skin notation is recommended based on evidence suggesting dermal absorption and adverse systemic effects in humans and animals.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***TWA: 10 ppm (30 mg/m^3)***
ACGIH	***2018***	***TLV-TWA: 5 ppm (15 mg/m^3)***

TLV-TWA protects against liver damage and irritation of the eyes and upper respiratory tract; derived from NOAEL (rats) and LOAEL (mice) of 25 ppm and supported by evidence showing no abnormal liver function tests in plant workers exposed at 5 ppm.

Summary of data:

Human data:

- Several studies reported irritation of eyes and upper respiratory tract
  - symptoms included watery eyes, coughing to chemical burns leading to fatal poisoning (2.7–20 ppm)
- Case reports and studies of high-dose exposures reported effects in liver function and digestive systems
  - symptoms included stomach pain, nausea, vomiting and epigastric cramps, skin irritation and rash
- Exposure causes increased alcohol intolerance
  - reported facial flushing and related symptoms after alcohol ingestion
  - maximum air level of DMF in workplace 200 ppm
- Estimated skin and lung vapour absorption at 40.4% and 59.6%, respectively
  - absorption of liquid through the skin likely greater contributor to total occupational exposure
- Long-term exposures (inhalation at 5 ppm and prevention of skin contact) by plant workers who handled DMF on a large scale did not have any health complaints nor experience abnormal liver function
- Cross-sectional studies of workers in synthetic leather factory exposed to air concentrations <10 ppm showed elevated liver enzymes (AST, ALT, γ-GTP and AP) compared to controls
  - authors concluded that exposures were increased due to accidental contact with liquid DMF and/or solvent vapour contact
- Worker exposures in acrylic fibre factory (0.3–15.5 ppm) found no difference in liver function between exposed vs control group
- Several studies in Asia reported effects in liver function and digestive system in exposed workers (inhalation of air concentrations ≤10 ppm)
  - studies not reliable due to uncertainties in study design methodology including lack of control group, failure to account for dermal exposures and/or concurrent high concentration peak exposures, co-exposures to other chemicals and limited reporting of air concentrations
- Testicular cancers reported (airframe repair shops and leather tannery) but not corroborated using cancer morbidity investigations among 3,859 male workers exposed between 1950 and 1970 at a Dupont facility (observed only one testicular cancer vs 1.7 expected)

Source	Year set	Standard

• Findings of genotoxicity studies in workers confounded due to co-exposures and/or smoking
• Limited reproductive studies and no developmental effects studies
  ○ Dose-dependent reduced sperm motility with urinary N-methylformamide but no association with air concentrations in workers exposed at 11.4 ± 3.9 ppm and 17.9 ± 8.9 ppm.
Animal data:
• LD_{50}: 3–7 g/kg (mice and rats, oral); low single-dose oral toxicity, liver as target organ
• LD_{50}: 3–11.5 mg/kg (rats, dermal)
  ○ slightly to moderately irritation to skin and eyes
  ○ can enhance absorption of other substances
• LC_{50}: 1,900–5,700 ppm (rats); inhalation exposures 1–7 h
• In a sub-chronic study involving whole-body exposures (30/sex/group), 6 dose groups (0, 50, 100, 200, 400, 800 ppm), 6 h/d, 5 d/wk for 13 wk):
  ○ NOAEC: 200 ppm (rats, both sexes)
  ○ NOAEC: 50 ppm (female mice) for absences of histopathological liver lesions
  ○ LOAEC: 50 ppm (male mice) for centrilobular hepatocellular hypertrophy and increased liver weights
• Combined oral and inhalation exposures markedly increased hepatocellular additive incidence and malignancy in a chronic bioassay involving inhalation exposures (50 male rats, 3 dose groups (0, 200, 400), 6 h/d, 5 d/wk for 2 yr)
• Negative results in *in vitro* and *in vivo* genotoxicity testing
• Reproductive and developmental toxicity observed in a range of species and routes of exposure but at doses higher than those causing liver and/or maternal toxicity.
 	
Insufficient data to recommend SEN notation or STEL.
A skin notation is recommended.
A3 classification (confirmed animal carcinogen) for carcinogenicity is supported by enough evidence in animals.		

DFG	***2016***	***MAK: 5 ppm (15 mg/m³)***

MAK value protects against effects in liver and developmental toxicity. Derived from NOAEC (rats) and LOAEC (mice) of 25 ppm and no effects observed in humans at 5 ppm (same as ACGIH).
Summary of additional data:
Animal data:
• Developmental effects following inhalation occur in concentration ranges which are also maternally toxic
  ○ NOAEC: 31 ppm (rats) and 50 ppm (rabbits)
  ○ oral NOAEL: 50 ppm and dermal NOAEL: 200 mg/kg (rats).		

SCOEL	***NA***	***NA***
No report.		
OARS/AIHA	***NA***	***NA***
No report.		

Source	Year set	Standard
HCOTN	***2011***	***Not assigned***
No additional information.		

Secondary source reports relied upon

Source		Year	Additional information
US EPA	✓	1990	Human data: • RfC 3×10^{-2} mg/m^3 derived from LOAEL: 220 mg/m^3, LOAEL (adj) and LOAEL (HEC) of 7.9 mg/m^3 from human occupational; studies to protect against digestive disturbances and minimal hepatic changes suggestive of liver abnormalities • Elevations of either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels indicative of liver disease in 36/58 employees exposed to large quantities (15–20 55-gallon drums/wk) in poorly ventilated area, 19 with twice normal levels.

Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic? No

The chemical is not a non-threshold based genotoxic carcinogen.

Notations

Source	Notations
SWA	Skin
HCIS	NA
NICNAS	NA
EU Annex	NA
ECHA	—
ACGIH	Carcinogenicity – A3, Skin,
DFG	Carcinogenicity – 4, H (skin)
SCOEL	NA
HCOTN	Carcinogenicity – category 2
IARC	Carcinogenicity – Group 2A
US NIOSH	NA

NA = not applicable (a recommendation has not been made by this Agency); — = the Agency has assessed available data for this chemical but has not recommended any notations

Skin notation assessment

Calculation	
Conclusion:	
Adverse effects in human case study:	yes
Dermal LD_{50} ≤1000 mg/kg:	yes
Dermal repeat-dose NOAEL ≤200 mg/kg:	
Dermal LD_{50}/Inhalation LD_{50} <10:	
In vivo dermal absorption rate >10%:	
Estimated dermal exposure at WES >10%:	
	a skin notation is warranted

IDLH

Is there a suitable IDLH value available?	Yes

Additional information

Molecular weight:	73.09
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 2.99 mg/m^3; 1 mg/m^3 = 0.335 ppm
This chemical is used as a pesticide:	☐
This chemical is a biological product:	☐
This chemical is a by-product of a process:	☐
A biological exposure index has been recommended by these agencies:	✓ ACGIH ✓ DFG ✓ SCOEL

Workplace exposure standard history

Year	Standard
1991	TWA: 10 ppm (30 mg/m^3)

References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7th Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the *TLVs® and BEIs® Guidelines section* on the ACGIH website.

European Chemicals Agency (ECHA) (2019) Dimethylformamide – REACH assessment.

Deutsche Forschungsgemeinschaft (DFG) (2017) Dimethylformamide – MAK value documentation.

Health Council of the Netherlands (HCOTN) (2011) N,N-dimethylformamide. Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2011/03OSH.

International Agency for Research on Cancer (IARC) (2018) Dimethylformamide. IARC Monographs on the evaluation of the carcinogenic risk to humans.

US. Environmental Protection Agency (US EPA). (1990). Chemical Assessment Summary – N,N-Dimethylformamide; CASRN 68-12-2. Integrated Risk Information System (IRIS).

US National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – dimethylformamide.