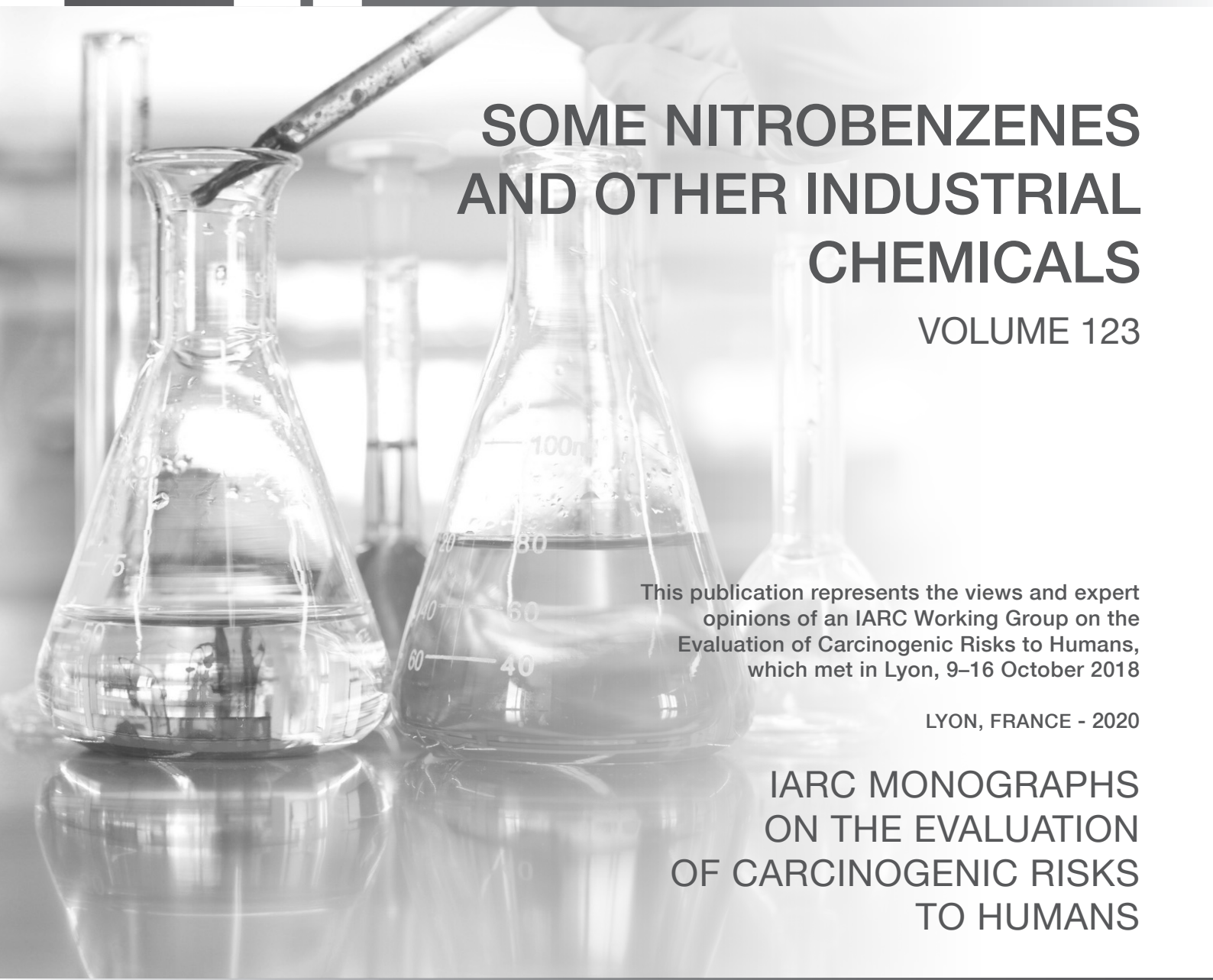
IARC MONOGRAPHS



SOME NITROBENZENES AND OTHER INDUSTRIAL CHEMICALS

VOLUME 123

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 9–16 October 2018

LYON, FRANCE - 2020

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

N,N-DIMETHYLACETAMIDE

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

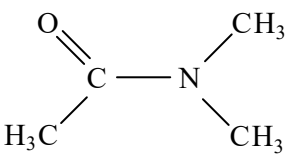
Chem. Abstr. Serv. Reg. No.: 127-19-5

Chem. Abstr. Serv. name: acetamide, *N*,*N*-dimethyl-

IUPAC systematic name: *N*,*N*-dimethylacetamide

Synonyms: acetic acid dimethylamide; acetic acid *N*,*N*-dimethylamide; dimethylacetamide; dimethylacetone amide; acetyldimethylamine.

1.1.2 Structural and molecular formulae, and relative molecular mass



Molecular formula: C_4H_9NO

Relative molecular mass: 87.12

1.1.3 Chemical and physical properties of the pure substance

Description: at room temperature, colourless liquid with a weak ammonia- or fish-like odour; stable; combustible; incompatible with strong oxidizing agents (PubChem, 2019)

Boiling point: 166 °C (Gescher & Threadgill, 1990)

Melting point: –20 °C (Gescher & Threadgill, 1990)

Volatility: vapour pressure, 2 mm Hg (0.27 kPa) at 25 °C (ChemSpider, 2015)

Flash point: 70 °C (Gescher & Threadgill, 1990)

Relative liquid density (water = 1): 0.9366 (25 °C/4 °C) (Gescher & Threadgill, 1990)

Flammable limits: upper explosion limit, 320 °F (160 °C), 11.5%; lower explosion limit, 212 °F (100 °C), 1.8% (NIOSH, 2016)

Solubility: soluble in water and most organic solvents (Gescher & Threadgill, 1990)

Conversion factor: 1 ppm = 3.563 mg/m^3 at normal temperature (25 °C) and pressure (101 kPa) (Gescher & Threadgill, 1990)

Technical products and impurities: available at purities of greater than 95% (ThermoFisher Scientific, 2018). Okuda et al. (2006) used *N*,*N*-dimethylacetamide of reagent grade (purity, > 99.9%) in a study in rats.

1.2 Production and use

1.2.1 Production

N,*N*-Dimethylacetamide is usually produced by the reaction of acetic acid with dimethylamine in a closed system at elevated temperature and pressure; the subsequent distillation purifies the product (ECHA, 2012).

1.2.2 Production volume

N,*N*-Dimethylacetamide has been listed as a chemical with a high production volume (OECD, 2009). In 2000, worldwide production of *N*,*N*-dimethylacetamide was between 50 000 and 60 000 tons per year [~45 360–54 430 metric tonnes per year] (OECD-SIDS, 2012).

In 2010, European production was reported to be around 15 000–20 000 tonnes, of which 85% was consumed in Europe (ECHA, 2012). In 1997, the consumption of *N*,*N*-dimethylacetamide in Japan was about 5000 tonnes per year (Nomiyama et al., 2000).

1.2.3 Use

In France, 1510 tonnes of *N*,*N*-dimethylacetamide are used per year in the preparation of chemical compounds, particularly for textile fibres and in the pharmaceutical sector (Honnert & Grzebyk, 2010). Worldwide, *N*,*N*-dimethylacetamide is mostly used (65–70%) as an intermediate in the production of agrochemicals, pharmaceuticals, fine chemicals, and as an excipient in human and veterinary pharmaceuticals (ECHA, 2012).

Approximately 20–25% of *N*,*N*-dimethylacetamide produced globally is used in the manufacture of synthetic textile fibres. It is also used as a solvent for several resins, including polyacrylonitrile, polyamides, and cellulose derivates, and in the manufacture of coatings, films, and other miscellaneous products (ECHA, 2012).

1.3 Methods of measurement and analysis

1.3.1 Air

N,*N*-Dimethylacetamide has been quantified in workplace air using a solid sorbent tube containing silica gel. Air is sampled at 0.01–1.0 L/min to give a sample volume of 15–80 L. Analysis was performed using gas chromatography (GC) with flame ionization detector. Silica gel has a high affinity for water, meaning that high relative humidity in the workplace may limit the use of this method (NIOSH, 1994).

Tanaka et al. (2002) described the measurement of *N*,*N*-dimethylacetamide in workplace air using liquid passive–diffusive samplers with analysis using GC with mass spectrometry or a flame thermionic detector. This method yielded data comparable to the United States National Institute of Occupational Safety and Health (NIOSH) silica gel tube method.

Diffusive samplers with activated charcoal adsorbent have also been used to measure exposure to *N*,*N*-dimethylacetamide (Spies et al., 1995a).

[The Working Group noted that the concentrations of *N*,*N*-dimethylacetamide in the air of working environments may not correctly express the intensity of the solvent uptake, as a substantial part occurs percutaneously. Consequently, the biological monitoring of exposure to *N*,*N*-dimethylacetamide is preferred to the study of the uptake of *N*,*N*-dimethylacetamide in different working facilities.]

1.3.2 Other environmental media

The measurement of *N*,*N*-dimethylacetamide at very low concentrations in water can be performed using a cartridge containing activated carbon fibre felt that is used for solid-phase extraction of different compounds in water, including *N*,*N*-dimethylacetamide.

The minimum detectable concentration of *N*,*N*-dimethylacetamide in water was reported to be 0.02 µg/L (Kawata et al., 2001).

1.3.3 Biomonitoring

Urinary concentration of *N*-methylacetamide has been shown to reflect systematic exposure to *N*,*N*-dimethylacetamide that may have entered the body by inhalation or through the skin, and is considered as a good biomarker for biological monitoring in professional exposure to *N*,*N*-dimethylacetamide (HSL, 2018). A good linear correlation between urinary concentrations of *N*-methylacetamide and urinary concentrations of *N*,*N*-dimethylacetamide has been demonstrated (Kawai et al., 1997; Perbellini et al., 2003). As shown in Section 4.1, Fig. 4.1, the first oxidation phase of *N*,*N*-dimethylacetamide yields *N*-hydroxymethyl-*N*-methylacetamide, which is slowly demethylated to *N*-methylacetamide. In practice, most of the *N*-hydroxymethyl-*N*-methylacetamide measured in urine is demethylated to *N*-methylacetamide during analysis by GC, because the GC injection port is maintained at a temperature of 250 °C or greater. Biological monitoring is normally based on the total urinary *N*-methylacetamide measured using this procedure (HSL, 2018). In addition, *N*-acetyl-*S*-(acetamidomethyl)-L-cysteine (another metabolite of *N*,*N*-dimethylacetamide) has been measured in the urine by Perbellini et al. (2003) and Princivalle et al. (2010).

Measurement of *N*,*N*-dimethylacetamide in plasma was proposed by Oechtering et al. (2006) and Cendana et al. (2017) to monitor exposure from drug therapies containing *N*,*N*-dimethylacetamide as a solvent. Oechtering et al. (2006) used a rapid and selective method involving plasma protein precipitation with trichloroacetic acid, followed by analysis by liquid chromatography with mass spectrometry. Results were accurate, precise, and reproducible in the range 0.25–150.0 mg/L of *N*,*N*-dimethylacetamide in plasma (Oechtering et al., 2006). Cendana et al. (2017) proposed the measurement of *N*,*N*-dimethylacetamide in plasma by precipitation of plasma proteins with acetonitrile, followed by high-performance liquid chromatography and ultraviolet detection. The limits of detection and quantification were 1 and 5 µg/mL respectively, with linearity between 1 and 1000 µg/mL.

1.4 Occurrence and exposure

1.4.1 Environmental occurrence

The release of *N*,*N*-dimethylacetamide to the environment during its production and processing occurs primarily as liquid effluent and gaseous emissions by venting (OECD-SIDS, 2001).

A global distribution model for persistent organic chemicals suggests that any release of *N*,*N*-dimethylacetamide into the air is relocated into water and soil (OECD-SIDS, 2012).

The principal sources of environmental release and possible population exposure in Europe are: to the air, about 650 tonnes per year related to fibre production; and liquid emissions, 350 tonnes per year related to water treatment, 950 tonnes per year from waste products or during maintenance or cleaning, and 450 tonnes per year as a result of residues in fibres (ECHA, 2012).

Despite using a very sensitive analytical method with a minimum detectable concentration of 0.02 µg/L in water, Kawata et al. (2001) were not able to find a detectable amount of *N*,*N*-dimethylacetamide in groundwater and in four river water samples in the Niigata Prefecture, Japan.

N,*N*-Dimethylacetamide undergoes rapid photochemical degradation in the atmosphere, with a half-life of 6.1 hours. Its bioaccumulation in aquatic species is very low because of its bioconcentration factor of 0.008. A low adsorption in soils and sediments can be assumed from

a calculated soil adsorption coefficient (K_{oc}) of 9.1. Several tests in sludges confirmed the biodegradability of *N*,*N*-dimethylacetamide in about 1 month. In soil, *N*,*N*-dimethylacetamide is easily mobilized by water without any possibility of volatilization (OECD-SIDS, 2001).

1.4.2 Exposure in the general population

N,*N*-Dimethylacetamide is used as a carrier in the intravenous formulation of some drugs. The compound was detected in the plasma of eight children who were given a single daily dose of intravenous busulfan, an alkylating agent used in blood transfusion or bone-marrow transplantation. Plasma concentrations of *N*,*N*-dimethylacetamide ranging from 110 to 198 µg/mL were measured 8 hours after the end of a 3-hour infusion, and peak plasma concentrations ranged from 158 to 438 µg/mL (Cendana et al., 2017).

Consumer exposure was reported to be negligible as suggested by results from migration tests with simulated sweating on textile articles containing residual *N*,*N*-dimethylacetamide (at 0.010–0.001%) (OECD-SIDS, 2001).

1.4.3 Occupational exposure

Human exposure to *N*,*N*-dimethylacetamide occurs mostly in workplaces where the substance is used downstream of its primary manufacture. [The Working Group noted that the manufacture of *N*,*N*-dimethylacetamide in a closed system does not favour the dispersion of the product in the workplace.]

In occupational settings, particularly downstream of production, the main routes of exposure are by inhalation and skin uptake. Table 1.1 and Table 1.2 summarize the workplace exposure to *N*,*N*-dimethylacetamide as measured in air and urine, respectively, reported in the literature.

Occupational inhalation exposures associated with the manufacture and processing of *N*,*N*-dimethylacetamide in Alabama, USA, were measured at up to 2.49 mg/m^3. Workers involved in resin preparation were exposed to *N*,*N*-dimethylacetamide at average concentrations of 9.30 mg/m^3 (maximum, 51.35 mg/m^3), and spinning operators had an average exposure of 7.02 mg/m^3 (maximum, 35.53 mg/m^3) (OECD-SIDS, 2001).

Spies et al. (1995a) monitored the exposure to *N*,*N*-dimethylacetamide of 127 employees from seven job classes in two departments of an acrylic-fibre manufacturing facility in the USA. *N*,*N*-Dimethylacetamide in workplace air was sampled with passive dosimeters worn on workers' lapels for the 12-hour shift. A total of 419 measurements of *N*,*N*-dimethylacetamide were made during 1 year. The arithmetic and geometric means were 2.0 and 1.45 ppm [7.13 and 5.17 mg/m^3] (averaged over 12 hours), respectively, with concentrations ranging from 0.2 to 25 ppm [0.71–89.08 mg/m^3]. The geometric standard deviation was 2.25 ppm [8.02 mg/m^3]. Results obtained on different working days were not significantly different. A positive association was observed between workplace *N*,*N*-dimethylacetamide air concentration and its metabolite *N*-methylacetamide in urine collected at the end of a 12-hour shift.

Perbellini et al. (2003) described workers exposed occupationally to low concentrations of *N*,*N*-dimethylacetamide (median not exceeding 1.5 ppm [< 5.3 mg/m^3]) while wearing light clothes (undershirt and shorts), which quickly became damp because of high humidity and temperature. In these conditions the skin uptake of *N*,*N*-dimethylacetamide was very high; about 20% of 233 urine samples provided by the workers at the end of their work shift had *N*-methylacetamide concentrations higher than 30 mg/g creatinine. The solvent adsorbed by sweat, which acted as a reservoir for skin uptake, continued throughout and after the work shift; a shower and a change of clothing at the end of the work shift ensured that dermal absorption of *N*,*N*-dimethylacetamide did not

Table 1.1 Workplace exposure to *N,N*-dimethylacetamide measured in air

Industry, country, year	Job and/or process	Mean (range) (mg/m³)[a]	Comments/additional data	Reference
Prefabricated synthetic products, Netherlands, 1997	Mechanical processing of the synthetic substance, produced elsewhere	52.52 (42.08–61.43) Average exposure of eight different workers: 21.73 (2.49–41.33), 33.49 (2.49–147.50), 47.74 (3.56–112.23), 51.66 (3.56–131.12), 79.10 (2.85–184.92), 78.39 (6.06–163.18), 48.46 (3.21–118.29), 39.19 (3.21–128.27)	Stationary monitoring with an infrared analyser for 7 days Personal sampling for six workers over an 8-h shift and two workers over a 4-h shift, over 5 subsequent working days	Borm et al. (1987)
Production of synthetic fibres, USA, 1989	Area where fibres containing *N,N*-dimethylacetamide were processed	Average exposure of five different workers: 4.56 (0.89–12.29), 5.20 (0.82–8.02), 3.81 (0.89–10.05), 3.35 (0.81–8.84), 3.81 (0.89–8.66)	Personal sampling for 5 days/week, over 4 subsequent working weeks	Kennedy & Pruett (1989)
Acrylic-fibre manufacturing facility, USA, 1995	Seven job classes in two departments	7.16 (0.71–89.08)	Data collected over 1 year from 30 workers who wore passive dosimeters during 12-h shifts	Spies et al. (1995a)

[a] Air concentrations given in ppm in the original publications were converted to mg/m³ by the Working Group using the conversion factor 1 ppm = 3.563 mg/m³

Table 1.2 Workplace exposure to *N,N*-dimethylacetamide as indicated by measurement of *N*-methylacetamide in urine

Industry, country, year	Job and/or process	Mean (range)	Comments/additional data	Reference
Production of synthetic fibres, USA, 1989	Area where fibres containing *N,N*-dimethylacetamide were processed	Average exposure of five different workers: 12.2 (4–31), 16.8 (6–42), 8.8 (4–15), 18.5 (7–42), 9.2 (1–20) mg/L	Urine samples provided at the end of 8-h work shifts for 5 days/week, for 4 subsequent working weeks	Kennedy & Pruett (1989)
Acrylic-fibre manufacturing facility, USA, 1995	Seven job classes in two departments	First day, end of 8-h shift: 15.4 (~1.8–280) mg/g creatinine Second day, end of 8-h shift: 18.9 mg/g creatinine	Data collected over 1 year from 30 workers who wore passive dosimeters during 12-h shifts	Spies et al. (1995a)
Elastane-fibre factories, Republic of Korea, 2002–2004	440 new workers were included as study subjects	19.6 (2.2–196.5) mg/g creatinine 5.2 (0.1–79.2) mg/g creatinine	503 urine samples from the eight departments in which 28 hepatic injuries induced by *N,N*-dimethylacetamide were found 464 urinary *N*-methylacetamide results from the other 11 departments without any hepatic injuries	Lee et al. (2006)
Factory producing acrylic fibres, Italy, 2003	223 workers from a chemical industry producing synthetic acrylic fibres (acrylic resin blended with *N,N*-dimethylacetamide was spun through about 600 small holes over an area of 100 cm^2 to produce acrylic fibres)	Median, 20.5 (1.5–173.6) mg/g creatinine	*N*-Methylacetamide concentrations were high in the urine of workers who had recently started up machinery; those attending the production control always had urinary *N*-methylacetamide < 30 mg/g creatinine	Perbellini et al. (2003)

continue, and reduced urinary concentrations of *N*-methylacetamide were measured the following morning.

1.5 Regulations and guidelines

Table 1.3 reports the occupational exposure limits for *N*,*N*-dimethylacetamide. A "skin" notation is identified in all regulations. Most countries propose the limit of 10 ppm (36 mg/m^3); exceptions to this include France and Germany (Deutsche Forschungsgemeinschaft), which propose 2 ppm (7.2 mg/m^3) and 5 ppm (18 mg/m^3), respectively (IFA, 2018).

Table 1.4 summarizes the biological monitoring limits for *N*-methylacetamide as a biological indicator index of exposure to *N*,*N*-dimethylacetamide.

1.6 Critical review of exposure assessment in key epidemiological studies

There were no studies in the literature specifically reporting on exposure assessment in key epidemiological studies. Spies et al. (1995a, b) and Lee et al. (2006) reported data on exposure to *N*,*N*-dimethylacetamide, but without any relationship to studies of cancer in humans. The single study of cancer in workers exposed to *N*,*N*-dimethylacetamide (Mastrangelo et al., 1993) used qualitative exposure categorization based on job tasks, work areas, and employment duration. [The Working Group considered this method insufficient to adequately characterize exposure in relation to risk of cancer.]

2. Cancer in Humans

2.1 Cohort studies

Mastrangelo et al. (1993) described a retrospective study of the mortality of 671 workers employed in an acrylic-fibre manufacturing facility in Venice, Italy. The process produced fibre for hosiery, clothing, and upholstery by dissolving polymerized acrylonitrile using *N*,*N*-dimethylacetamide, and then spinning the paste to form the fibre. The facility began manufacturing in 1959, and workers employed for more than 1 year before 1988 were recruited into the cohort; clerks and those with past exposure to vinyl chloride or benzidine (classified as Group 1 by IARC, as causes of cancer of the liver and bladder, respectively) were excluded. Workers were grouped according to work area and job task, reflecting presumed differences in exposure levels, and into categories of duration of exposure and time since first exposure. Workers were followed until 1990.

There were a small number of deaths (32 observed, 31.2 expected), and statistically significant increased risks were observed only for cancers of the intestine and colon (4 deaths, 0.38 expected [standardized mortality rate, 10.5; 95% confidence interval (CI), 2.9–27.0]) or for death from "ill-defined symptoms". The number of deaths from cancers of the intestine and colon was significantly increased in the subgroup with a short duration of exposure (< 4 years) and in the subgroup with less than 9 years since first exposure.

Perbellini et al. (2003) investigated the exposure in the workforce in this factory around 10 years after completion of the epidemiological study. Concentrations of *N*,*N*-dimethylacetamide in air were low (< 1.5 ppm) at this time, but median concentration of *N*-methylacetamide in urine was 20.5 mg/g creatinine with about 20% of measurements greater than 30 mg/g creatinine. [The Working Group noted that these

Table 1.3 International occupational exposure limit values for *N,N*-dimethylacetamide

Country or region	8-h limit		Short-term limit	
	ppm	mg/m³	ppm	mg/m³
Australia	10	36		
Austria	10	36	20	72
Belgium	10[a]	36	20[a]	72[a]
Canada, Ontario	10			
Canada, Province of Québec	10	36		
China		20		
Denmark	10	35	20	70
European Union[b]	10	36	20[a]	72[a]
Finland	10	36	20[a]	72[a]
France[c]	2	7.2	10[a]	36[a]
Germany (AGS)	5	18	10[a]	36[a]
Germany (DFG)	5	18	10[a]	36[a]
Hungary		36		72
Ireland	10	36	20[c]	72[c]
Italy[d]	10	36	20	72
Japan (JSOH)	10	36		
Latvia	10	36	20[a]	72[a]
Netherlands		36		72
New Zealand	10	36		
Republic of Korea	10	35		
Romania	10	36	20[a]	72[a]
Singapore	10	36		
Spain	10	36	20	72
Sweden	10	35	20[a]	70[a]
Switzerland	10	35	20	70
Turkey	10	36	20[a]	72[a]
UK	10	36	20	72
USA (NIOSH)	10	35		
USA (OSHA)	10	35		

AGS, Ausschuss für Gefahrstoffe; DFG, Deutsche Forschungsgemeinschaft; JSOH, Japan Society for Occupational Health; NIOSH, United States National Institute for Occupational Safety and Health; OSHA, United States Occupational Safety and Health Administration

[a] 15-minute average value

[b] Indicative occupational exposure limit value (IOELV)

[c] 15-minute reference period

[d] Skin

From IFA (2018)

Table 1.4 Occupational exposure to *N*,*N*-dimethylacetamide: biological exposure limits for urinary *N*-methylacetamide

Country	Year	Concentration	Sampling time and notation
Germany (DFG)	2017	30 mg/g creatinine (*N*-methylacetamide plus *N*-hydroxymethyl-*N*-methylacetamide)	End of exposure after several shifts
UK	2017	64 mg/g creatinine[a]	
USA (ACGIH)	2017	30 mg/g creatinine	End of shift at the end of the working week

ACGIH, American Conference of Governmental Industrial Hygienists; DFG, Deutsche Forschungsgemeinschaft
[a] 100 mmol *N*-methylacetamide per mol creatinine (conversion, 1 mmol/mol = 0.646 mg/g)
Compiled from HSL (2018)

findings suggest high dermal absorption of *N*,*N*-dimethylacetamide.]

[The Working Group noted that the study by Mastrangelo et al. (1993) found an excess of some cancers in this workforce. However, the association between these cancers and *N*,*N*-dimethylacetamide exposure is unclear, given the study's crude exposure assessment methodology. The Working Group also noted that the study population was relatively young and the number of expected deaths from cancer was small. It is unclear whether data from the Perbellini et al. (2003) study are representative of historical conditions in the factory.]

2.2 Case–control studies

No case–control studies of occupational exposure to *N*,*N*-dimethylacetamide were available to the Working Group.

3. Cancer in Experimental Animals

See Table 3.1

3.1 Mouse

Inhalation

Groups of 78 male and 78 female Crl:CD-1 (ICR) mice (age, 49 days) were exposed to *N*,*N*-dimethylacetamide (purity, 99.9%) at a concentration of 0 (control), 25, 100, or 350 ppm by whole-body inhalation for 6 hours per day, 5 days per week, for 18 months (Malley et al., 1995). Five males and five females per group were killed at 2–3 weeks, 3 months, and 12 months. There was a slight decrease in survival in females at 350 ppm. Survival rates in males were 46% (control), 60% (25 ppm), 54% (100 ppm), and 41% (350 ppm); respective survival rates in females were 80%, 77%, 76%, and 60%. Male mice at 100 and 350 ppm had a tendency towards higher body weight over the course of the 18-month exposure period. Female mice at 350 ppm had a significantly higher body weight compared with the control group for the first 9 months; body weights after 9 months were comparable to those of the control group. Full histopathology was performed on all major organs in the groups exposed at 0 and 350 ppm; lungs, liver, kidneys, and all gross lesions from mice in the groups at 25 and 100 ppm were also examined microscopically. There was no significant increase in the incidence of any tumour in either male or female mice. Regarding non-neoplastic lesions, there was a significant increase in the incidence of centrilobular hepatocellular hypertrophy

Table 3.1 Studies of carcinogenicity with *N,N*-dimethylacetamide in experimental animals

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. (or %) of surviving animals	Incidence or multiplicity of tumours	Significance	Comments
Full carcinogenicity Mouse, Crl:CD-1 (ICR) (M) 49 d 18 mo Malley et al. (1995)	Whole-body inhalation 99.9% Air 0, 25, 100, 350 ppm for 6 h/d, 5 d/wk 78, 78, 78, 78 46%, 60%, 54%, 41%	*Liver* Hepatocellular adenoma 14/64, 12/64, 10/64, 8/65 Hepatocellular carcinoma 2/64, 5/64, 4/64, 1/65 Haemangiosarcoma 0/64, 1/64, 0/64, 2/65 *Testis:* interstitial cell tumour 0/64, 0/30, 1/39, 1/65	 NS NS NS NS	Principal strengths: covered most of the lifespan; multiple dose study; males and females used; high number of mice per group Principal limitations: inconsistencies in numbers of mice reported throughout the article The denominator represents the number of mice investigated for this tumour type; five males and five females per group were killed at 2–3 wk, 3 mo, and 12 mo
Full carcinogenicity Mouse, Crl:CD-1 (ICR) (F) 49 d 18 mo Malley et al. (1995)	Whole-body inhalation 99.9% Air 0, 25, 100, 350 ppm for 6 h/d, 5 d/wk 78, 78, 78, 78 80%, 77%, 76%, 60%	*Liver* Hepatocellular adenoma 0/63, 0/64, 0/63, 1/65 Haemangiosarcoma 0/63, 2/64, 0/63, 1/65 *Mammary gland:* adenocarcinoma 0/59, 1/17, 0/15, 1/59	 NS NS NS	Principal strengths: covered most of the lifespan; multiple dose study; males and females used; high number of mice per group Principal limitations: inconsistencies in numbers of mice reported throughout the article The denominator represents the number of mice investigated for this tumour type; five males and five females per group were killed at 2–3 wk, 3 mo, and 12 mo
Full carcinogenicity Mouse, B6D2F$_1$/Crlj (M) 6 wk 104 wk JBRC (2013b)	Whole-body inhalation 99.9% Air 0, 12, 60, 300 ppm for 6 h/d, 5 d/wk 50, 50, 50, 50 35, 40, 33, 32	*Liver* Hepatocellular adenoma 10/50, 8/50, 7/50, 28/50* Hepatocellular carcinoma 7/50, 4/50, 2/50, 3/50 Hepatocellular adenoma or carcinoma (combined)	 $P \leq 0.0001$, Peto trend test prevalence method, Peto trend test combined analysis, Cochran–Armitage trend test; NS, Peto trend test standard method; *$P = 0.0002$, Fisher exact test NS	Principal strengths: well-conducted GLP study; multiple dose study; males and females used Historical control incidence (range) in B6D2F$_1$/Crlj male mice: hepatocellular adenoma or carcinoma, 35.2% (8–68%); lymph node, malignant lymphoma, 12.5% (2–28%)

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. (or %) of surviving animals	Incidence or multiplicity of tumours	Significance	Comments
Full carcinogenicity Mouse, B6D2F$_1$/Crlj (M) 6 wk 104 wk JBRC (2013b) (cont.)		16/50 (32%), 12/50 (24%), 9/50 (18%), 29/50 (58%)*	$P \leq 0.0001$, Peto trend test prevalence method, Peto trend test combined analysis, Cochran–Armitage trend test; NS, Peto trend test standard method; *$P < 0.01$, Fisher exact test	
		Histiocytic sarcoma		
		1/50, 4/50, 4/50, 3/50	NS	
		Haemangiosarcoma		
		0/50, 3/50, 2/50, 0/50	NS	
		Lymph node: malignant lymphoma		
		7/50 (14%), 8/50 (16%), 8/50 (16%), 12/50 (24%)	$P < 0.05$, Peto trend test combined analysis; NS, Peto trend test standard method, Peto trend test prevalence method, Cochran–Armitage trend test	
Full carcinogenicity Mouse, B6D2F$_1$/Crlj (F) 6 wk 104 wk JBRC (2013b)	Whole-body inhalation 99.9% Air 0, 12, 60, 300 ppm for 6 h/d, 5 d/wk 50, 50, 50, 50 21, 25, 21, 22	*Liver*		Principal strengths: well-conducted GLP study; multiple dose study; males and females used Incidence in historical controls (range): pituitary adenoma, 14.4% (2–34%); pituitary adenocarcinoma, 0.6% (0–4%); pituitary adenoma or adenocarcinoma, 15.0% (2–34%)
		Hepatocellular adenoma		
		2/50, 2/50, 4/50, 35/50*	$P < 0.0001$, Peto trend test prevalence method, Cochran–Armitage trend test; *$P < 0.0001$, Fisher exact test	
		Hepatocellular carcinoma		
		0/50, 1/50, 0/50, 8/50*	$P < 0.0001$, Peto trend test prevalence method, Cochran–Armitage trend test; *$P = 0.0029$, Fisher exact test	
		Hepatocellular adenoma or carcinoma (combined)		
		2/50, 3/50, 4/50, 37/50*	$P < 0.0001$, Peto trend test prevalence method, Cochran–Armitage trend test; *$P < 0.0001$, Fisher exact test	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. (or %) of surviving animals	Incidence or multiplicity of tumours	Significance	Comments
Full carcinogenicity Mouse, B6D2F$_1$/Crlj (F) 6 wk 104 wk JBRC (2013b) (cont.)		*Pituitary gland* Adenoma 8/48 (16.7%), 6/50 (12%), 11/50 (22%), 8/50 (16%)	$P = 0.0027$, Peto trend test standard method; NS, Peto trend test prevalence method, Peto trend test combined analysis, Cochran–Armitage trend test	
		Adenocarcinoma 0/48, 0/50, 1/50, 1/50	NS	
		Adenoma or adenocarcinoma (combined) 8/48 (16.7%), 6/50 (12%), 12/50 (24%), 9/50 (18%)	$P = 0.0027$, Peto trend test standard method; NS, Peto trend test prevalence method, Peto trend test combined analysis, Cochran–Armitage trend test	
Full carcinogenicity Rat, Crl:CD (M) 43 d 24 mo Malley et al. (1995)	Whole-body inhalation 99.9% Air 0, 25, 100, 350 ppm for 6 h/d, 5 d/wk 78, 78, 78, 78 28%, 25%, 29%, 40%	*Liver* Hepatocellular adenoma 3/65, 3/63, 2/63, 1/62	NS	Principal strengths: covers most of the lifespan; multiple dose study; males and females used; high number of rats per group Principal limitations: inconsistencies in numbers of rats reported throughout the article. The article reported that the number of animals per group at start was 87, which the Working Group believed was a misprint of 78 The denominator represents the number of rats investigated for this tumour type; five males and five females per group killed at 2–3 wk, 3 mo, and 12 mo
		Hepatocellular carcinoma 1/65, 0/63, 1/63, 1/62	NS	
		Testis: interstitial cell adenoma 7/65, 6/53, 8/50, 4/62	NS	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. (or %) of surviving animals	Incidence or multiplicity of tumours	Significance	Comments
Full carcinogenicity Rat, Crl:CD (F) 43 d 23.5 mo Malley et al. (1995)	Whole-body inhalation 99.9% Air 0, 25, 100, 350 ppm for 6 h/d, 5 d/wk 78, 78, 78, 78 18%, 29%, 26%, 32%	*Liver* Hepatocellular adenoma 0/62, 0/62, 1/62, 0/64 Hepatocellular carcinoma 0/62, 0/62, 0/62, 0/64	 NS NA	Principal strengths: covers most of the lifespan; multiple dose study; males and females used; high number of rats per group Principal limitations: inconsistencies in numbers of rats reported throughout the article. The article reported that the number of animals per group at start was 87, which the Working Group believed was a misprint of 78 The denominator represents the number of rats investigated for this tumour type; five males and five females per group killed at 2–3 wk, 3 mo, and 12 mo
Full carcinogenicity Rat, F344/DuCrlCrlj (M) 6 wk 104 wk JBRC (2013d)	Whole-body inhalation 99.9% Air 0, 18, 90, 450 ppm for 6 h/d, 5 d/wk 50, 50, 50, 50 38, 41, 39, 40	*Liver* Hepatocellular adenoma 1/50, 1/50, 1/50, 9/50* Hepatocellular carcinoma 0/50, 0/50, 0/50, 4/50 (8%) Hepatocellular adenoma or carcinoma (combined)	 $P < 0.0001$, Peto trend test prevalence method, Cochran–Armitage trend test; *$P = 0.0078$, Fisher exact test $P \leq 0.0006$, Peto trend test prevalence method, Cochran–Armitage trend test	Principal strengths: well-conducted GLP study; multiple dose study; males and females used Incidence in historical controls (range): hepatocellular adenoma, 2.1% (0–12%); hepatocellular carcinoma, 0.5% (0–4%); hepatocellular adenoma or carcinoma, 2.5% (0–14%); adrenal gland, pheochromocytoma, 326/2847 (11.5%) (0–40%)

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. (or %) of surviving animals	Incidence or multiplicity of tumours	Significance	Comments
Full carcinogenicity Rat, F344/DuCrlCrlj (M) 6 wk 104 wk JBRC (2013d) (cont.)		1/50, 1/50, 1/50, 12/50*	$P < 0.0001$, Peto trend test prevalence method, Cochran–Armitage trend test; *$P = 0.0009$, Fisher exact test	
		Adrenal gland		
		Pheochromocytoma		
		2/50 (4%), 1/50 (2%), 1/50 (2%), 5/50 (10%)	$P < 0.04$, Peto trend test prevalence method, Cochran–Armitage trend test	
		Pheochromocytoma or malignant pheochromocytoma (combined)		
		4/50, 3/50, 1/50, 6/50	NS	
Full carcinogenicity Rat, F344/DuCrlCrlj (F) 6 wk 104 wk JBRC (2013d)	Whole-body inhalation 99.9% Air 0, 18, 90, 450 ppm for 6 h/d, 5 d/wk 50, 50, 50, 50 41, 39, 36, 45	*Liver*		Principal strengths: well-conducted GLP study; multiple dose study; males and females used
		Hepatocellular adenoma		
		2/50, 0/50, 2/50, 0/50	NS	
		Hepatocellular carcinoma		
		0/50, 0/50, 0/50, 1/50	NS	
Initiation–promotion (tested as promoter) Hamster, Syrian golden (F) ~1 mo 6 wk McGaughey & Jensen (1980)	Application on the cheek pouch NR DMSO 0.2% DMBA 3×/wk for 4 wk, followed by 0.05 M retinyl acetate plus 0 (control) or 0.1 M *N*,*N*-dimethylacetamide 3×/wk for 6 wk 10, 10 10, 10	*Oral mucosa*		Principal limitations: use of a single dose; low dose used; short duration of exposure; only one sex used; exact amount of chemicals applied unknown Plaques are putative non-neoplastic lesions
		Total "tumours" (including plaques)		
		10/10, 10/10	NS	
		5.70 ± 1.19, 3.90 ± 0.67	NS	
		Advanced "tumours" (excluding plaques)		
		7/10, 5/10	NS	
		2.20 ± 0.55, 1.00 ± 0.39	NS	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. (or %) of surviving animals	Incidence or multiplicity of tumours	Significance	Comments
Initiation–promotion (tested as promoter) Hamster, Syrian golden (F) ~1 mo 6 wk McGaughey & Jensen (1980)	Application on the cheek pouch NR DMSO 0.2% DMBA 3×/wk for 4 wk, followed by 0.5% croton oil plus 0 (control) or 0.1 M *N*,*N*-dimethylacetamide 3×/wk for 6 wk 10, 10 10, 9	*Oral mucosa* Total "tumours" (including plaques) 10/10, 7/9 6.00 ± 1.05, 3.00 ± 1.00 Advanced "tumours" (excluding plaques) 5/10, 1/9 1.00 ± 0.42, 0.22 ± 0.22	 NS NS NS NS	Principal limitations: use of single dose; low dose used; short duration of exposure; only one sex used; exact amount of chemicals applied unknown Plaques are putative non-neoplastic lesions

d, day; DMBA, 7,12-dimethylbenz[*a*]anthracene; DMSO, dimethyl sulfoxide; F, female; GLP, good laboratory practice; M, male; mo, month; NA, not applicable; NR, not reported; NS, not significant; ppm, parts per million; wk, week

and hepatic Kupffer cell pigment accumulation in males at 350 ppm, and of hepatic single-cell necrosis in females at 350 ppm (Malley et al., 1995). [The Working Group noted that the study covered most of the lifespan, was conducted using multiple doses in males and females, and used a high number of mice per group. However, a limitation of the study was the inconsistency in the numbers of mice reported throughout the article.]

In a study that complied with good laboratory practice (GLP), groups of 50 male and 50 female B6D2F$_1$/Crlj mice (age, 6 weeks) were exposed to *N*,*N*-dimethylacetamide (purity, 99.9%) at a concentration of 0 (control), 12, 60, or 300 ppm by whole-body inhalation for 6 hours per day, 5 days per week, for 104 weeks (JBRC, 2013a, b). The survival rate was not affected by the treatment. Survival rates in males were 35/50 (control), 40/50 (12 ppm), 33/50 (60 ppm), and 32/50 (300 ppm); respective survival rates in females were 21/50, 25/50, 21/50, and 22/50. A significant decrease in body-weight gain was observed in males at 300 ppm throughout the exposure period (9% lower at the end of the exposure period). No significant difference in body-weight gain was observed in females. All mice, including those found dead or in a moribund state, as well as those surviving to the end of the 2-year exposure period, underwent complete necropsy.

In males, the incidence of hepatocellular adenoma (10/50, 8/50, 7/50, and 28/50) was significantly increased in mice at 300 ppm ($P = 0.0002$, Fisher exact test) compared with controls. The incidence of hepatocellular adenoma or carcinoma (combined) – 16/50 (32%), 12/50 (24%), 9/50 (18%), and 29/50 (58%) – was significantly increased in mice at 300 ppm ($P < 0.01$, Fisher exact test) compared with controls, but within the historical control range (incidence, 35.2%; range, 8–68%). The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) occurred with significant positive trends ($P \leq 0.0001$, Peto trend test prevalence method, Peto trend test combined analysis, and Cochran–Armitage trend test; not significant by Peto trend test standard method). The incidence of hepatocellular carcinoma (7/50, 4/50, 2/50, and 3/50) was not significantly increased. [Although the Working Group considered the increased incidence of hepatocellular adenoma to be related to treatment, the increased incidence of hepatocellular adenoma or carcinoma (combined) was not considered to be related to treatment because it was driven by the increase in the incidence of hepatocellular adenoma.] There was a significant positive trend in the incidence of malignant lymphoma of the lymph node (7/50 (14%), 8/50 (16%), 8/50 (16%), and 12/50 (24%); $P < 0.05$, Peto trend test combined analysis; not significant by Peto trend test standard method, Peto trend test prevalence method, and Cochran–Armitage trend test); all these incidences were within the range for historical controls (incidence, 12.5%; range, 2–28%). [The Working Group considered that the positive trend in the incidence of malignant lymphoma could not be linked to the treatment because statistical analyses were inconclusive and all incidences were within the range for historical controls.]

In females, the incidence of hepatocellular adenoma (2/50, 2/50, 4/50, and 35/50) was significantly increased in mice at 300 ppm ($P < 0.0001$, Fisher exact test) compared with controls. The incidence of hepatocellular carcinoma (0/50, 1/50, 0/50, and 8/50) was significantly increased in mice at 300 ppm ($P = 0.0029$, Fisher exact test) compared with controls. The incidence of hepatocellular adenoma or carcinoma (combined) (2/50, 3/50, 4/50, and 37/50) was significantly increased in mice at 300 ppm ($P < 0.0001$, Fisher exact test) compared with controls. The incidence of hepatocellular adenoma, hepatocellular carcinoma, and of hepatocellular adenoma or carcinoma (combined) occurred with significant positive trends ($P < 0.0001$, Peto trend test prevalence method and Cochran–Armitage trend test).

The incidence of adenoma of the pituitary gland (8/48 (16.7%), 6/50 (12%), 11/50 (22%), and 8/50 (16%)) was not significantly increased in treated-females (not significant, Fisher exact test). There was a significant positive trend in the incidence of adenoma of the pituitary gland (P = 0.0027, Peto trend test standard method) that was not detected by other trend tests (not significant by Peto trend test prevalence method, Peto trend test combined analysis, and Cochran–Armitage trend test); all incidences were within the range for historical controls (incidence, 14.4%; range, 2–34%). The incidence of adenocarcinoma of the pituitary gland (0/48, 0/50, 1/50, and 1/50) was not significantly increased. The incidence of adenoma or adenocarcinoma (combined) of the pituitary gland – 8/48 (16.7%), 6/50 (12%), 12/50 (24%), and 9/50 (18%) – was not significantly (Fisher exact test) increased in treated females compared with controls. However, there was a significant positive trend in the incidence of adenoma or adenocarcinoma (combined) of the pituitary gland (P = 0.0027, Peto trend test standard method) that was not detected by other trend tests (not significant by Peto trend test prevalence method, Peto trend test combined analysis, and Cochran–Armitage trend test), but all incidences were within the range for historical controls (incidence, 15.0%; range, 2–34%). [The Working Group considered that the positive trend in the incidence of adenoma and of adenoma or adenocarcinoma (combined) of the pituitary gland could not be linked to the treatment because statistical analyses were inconclusive and all incidences were within the range for historical controls.]

Regarding non-neoplastic lesions, there was a significant increase in the incidence of eosinophilic foci in the liver in males and females at 300 ppm (JBRC, 2013a, b). [The Working Group noted that this was a well-conducted GLP study with the use of multiple doses, a high number of mice per group, and males and females.]

3.2 Rat

Inhalation

Groups of 87 male and 87 female [the Working Group believed 87 was a misprint of 78 in both cases] Crl:CD rats (age, 43 days) were exposed to *N*,*N*-dimethylacetamide (purity, 99.9%) at a concentration of 0 (control), 25, 100, or 350 ppm by whole-body inhalation for 6 hours per day, 5 days per week, for 24 months in males and 23.5 months in females (Malley et al., 1995). Five males and five females per group were killed at 2–3 weeks, 3 months, and 12 months. There was a slight non-significant increase in survival in males at 350 ppm and in all treated females. Survival rates in males were 28% (control), 25% (25 ppm), 29% (100 ppm), and 40% (350 ppm); respective survival rates in females were 18%, 29%, 26%, and 32%. A compound-related decrease in body weight and body-weight gain was observed in males (body-weight gain, 16% lower) and females (body-weight gain, 17% lower) at 350 ppm. Full histopathology was performed on all major organs in the rats at 0 and 350 ppm; lungs, liver, kidneys, and all gross lesions from rats in the groups at 25 and 100 ppm were also examined microscopically. There was no significant compound-related increase in the incidence of any tumours in either male or female rats. Regarding non-neoplastic lesions, there was a significant increase in the incidence of hepatic focal cystic degeneration in males at 100 and 350 ppm, of biliary hyperplasia and hepatic peliosis in males at 350 ppm, and of hepatic accumulation of lipofuscin and/or haemosiderin in males and females at 350 ppm (Malley et al., 1995). [The Working Group noted that the study covered most of the lifespan and was conducted with multiple doses, in both males and females, and with a high number of rats per group; data on survival rate and body weight throughout the study were provided in graphic form. However, a limitation of the study was the inconsistencies

in the numbers of rats reported throughout the article.]

In a study that complied with GLP, groups of 50 male and 50 female Fischer 344/DuCrlCrlj rats (age, 6 weeks) were exposed to *N*,*N*-dimethylacetamide (purity, 99.9%) at a concentration of 0 (control), 18, 90, or 450 ppm by whole-body inhalation for 6 hours per day, 5 days per week, for 104 weeks (JBRC, 2013c, d). The survival rate was not affected by the treatment. Survival rates in males were 38/50 (control), 41/50 (18 ppm), 39/50 (90 ppm), and 40/50 (450 ppm); respective survival rates in females were 41/50, 39/50, 36/50, and 45/50. A significant decrease in body weight was observed throughout the exposure period in males (16% lower at the end of the exposure period) and females (9% lower at the end of the exposure period) at 450 ppm. All rats, including those found dead or in a moribund state, as well as those surviving to the end of the 2-year exposure period, underwent complete necropsy.

In males, the incidence of hepatocellular adenoma (1/50, 1/50, 1/50, and 9/50; $P < 0.0001$, Peto trend test prevalence method and Cochran–Armitage trend test) was significantly increased in rats at 450 ppm ($P = 0.0078$, Fisher exact test) compared with controls. The incidence of hepatocellular carcinoma (0/50, 0/50, 0/50, and 4/50) was not statistically different (by Fisher exact test), but the increase in the incidence in the group exposed at the highest dose was above the upper bound of the range for historical controls (incidence, 13/2848 (0.5%); range, 0–4%). The incidence of hepatocellular adenoma or carcinoma (combined) – 1/50 (2%), 1/50 (2%), 1/50 (2%), and 12/50 (24%) – was significantly increased in rats at 450 ppm ($P = 0.0009$, Fisher exact test) compared with controls; the incidence in the group at the highest dose was above the upper bound of the range for historical controls (incidence, 2.5%; range, 0–14%). The incidence of hepatocellular adenoma, hepatocellular carcinoma, and of hepatocellular adenoma or carcinoma (combined) occurred with significant positive trends ($P \leq 0.0006$, Peto trend test prevalence method and Cochran–Armitage trend test). There was a significant positive trend ($P < 0.04$, Peto trend test prevalence method and Cochran–Armitage trend test) in the incidence of pheochromocytoma of the adrenal gland – 2/50 (4%), 1/50 (2%), 1/50 (2%), and 5/50 (10%) – but all were below the average reported in the historical control database (326/2847 (11.5%); range; 0–40%). [The Working Group considered that the incidence of pheochromocytoma of the adrenal gland was not increased by the treatment because the incidences were below the average reported in the historical control database.]

In females, there was no significant increase in tumour incidence in any of the treated groups compared with controls.

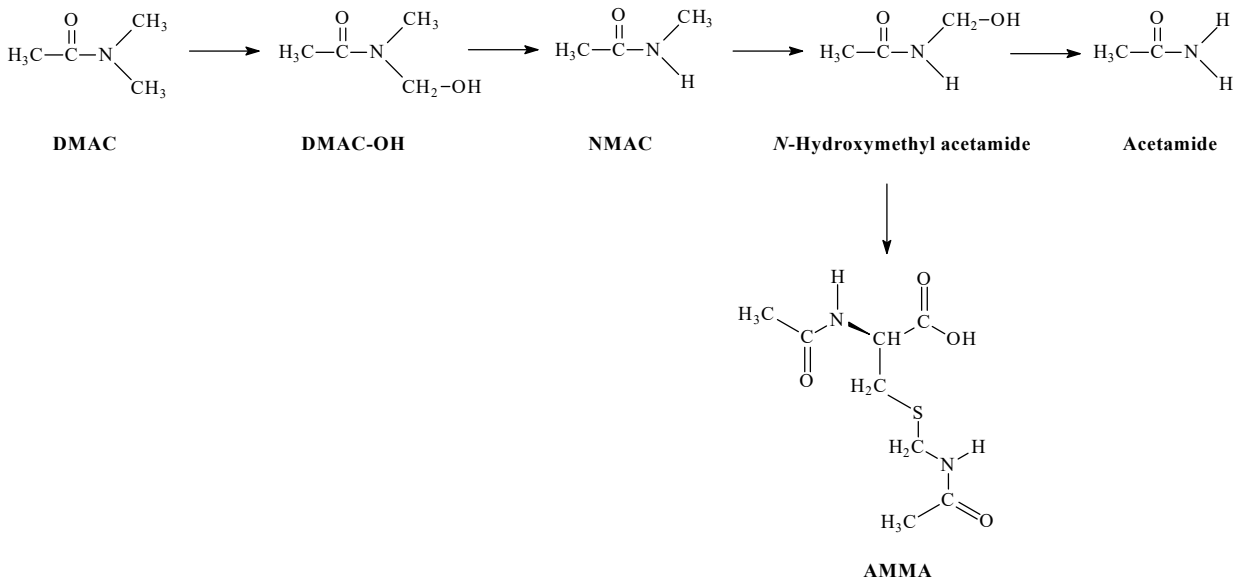
Regarding non-neoplastic lesions, there was a significant increase in the incidence of eosinophilic foci in the liver in males at 450 ppm, of hepatic clear cell foci in females at 450 ppm, of hepatic Kupffer cell pigment accumulation in males at 450 ppm and in females at 90 and 450 ppm, and of focal fatty degeneration in the liver in males at 90 and 450 ppm (JBRC, 2013c, d). [The Working Group noted this was a well-conducted GLP study with the use of multiple doses, a high number of rats per group, and males and females.]

3.3 Hamster

Initiation–promotion (tested as promoter)

A total of four groups of 10 female Syrian golden hamsters (age, ~1 month) were treated by painting the right cheek pouches with 0.2% 7,12-dimethylbenz[*a*]anthracene (DMBA) in dimethyl sulfoxide (DMSO) using cotton-tipped applicator sticks, 3 times per week for 4 weeks. This was followed by painting either with 0.05 M retinyl acetate or 0.5% croton oil in DMSO, plus painting either with DMSO (con-

Fig. 4.1 Proposed metabolic scheme for *N,N*-dimethylacetamide



AMMA, *S*-(acetamidomethyl)mercapturic acid; DMAC, *N,N*-dimethylacetamide; DMAC-OH, *N*-hydroxymethyl-*N*-methylacetamide; NMAC, *N*-methylacetamide

From ACGIH®, Documentation of the Threshold Limit Values and Biological Exposure Indices, 7th Edition. Copyright 2001. Reprinted with permission (Yamamoto et al., 2018)

trol) or 0.1 M *N,N*-dimethylacetamide [purity, not reported] in DMSO, 3 times per week, for another 6 weeks. *N,N*-Dimethylacetamide did not increase the incidence or multiplicity of total oral mucosa "tumours" and of advanced oral mucosa "tumours" (all oral mucosa "tumours" except plaques [putative preneoplastic lesions]) compared with the incidence and multiplicity for the groups treated with DMBA plus retinyl acetate only or DMBA plus croton oil only (McGaughey & Jensen, 1980). [The Working Group noted that the limitations of the study included the short-duration two-stage design, the small number of hamsters per group, the use of only one sex and a single dose, and the lack of precise information about the exact amount of chemicals applied.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

See Fig. 4.1

Biomonitoring studies of exposed workers have provided information about the metabolism of *N,N*-dimethylacetamide (Spies et al., 1995a; Perbellini et al., 2003; Yamamoto et al., 2018). [Because biomonitoring studies using GC can be confounded by thermal degradation of certain metabolites during analysis (Perbellini et al., 2003; Yamamoto et al., 2018), the Working Group considered other analytical methods to evaluate possible *N,N*-dimethylacetamide urinary metabolites.] Analysis of urine using liquid chromatography and tandem mass spectrometry has shown that *N,N*-dimethylacetamide

is metabolized to *N*-hydroxymethyl-*N*-methylacetamide, *N*-methylacetamide, *N*-hydroxymethylacetamide, acetamide, and *S*-(acetamidomethyl)mercapturic acid, with *N*-hydroxymethyl-*N*-methylacetamide being the most commonly identified metabolite (Yamamoto et al., 2018). Nomiyama et al. (2000) exposed healthy men to *N*,*N*-dimethylacetamide at 6.1 ± 1.3 (mean ± standard deviation, SD) ppm for 4 hours under one of two sets of experimental conditions: whole-body while breathing fresh air (to estimate dermal absorption) or via a face mask (to estimate inhalation absorption). Mean dermal and lung absorption were estimated to be 40.4% and 59.6% of the total *N*,*N*-dimethylacetamide uptake, respectively. Mean biological half-lives of urinary *N*-methylacetamide were 9.0 ± 1.4 and 5.6 ± 1.3 hours via skin and lung, respectively (Nomiyama et al., 2000). Maxfield et al. (1975) also performed inhalation (10 ppm for 6 hours via face mask) and dermal exposure studies with human subjects. *N*,*N*-Dimethylacetamide absorption was estimated to be 30% via the skin and 70% via the lung (Maxfield et al., 1975). Dermal absorption of *N*,*N*-dimethylacetamide also occurs in workers and has been estimated as 13–30% (Borm et al., 1987). Most (n = 6) workers studied (n = 8) excreted about 13% of the calculated inhaled dose as metabolite in urine, and the half-life of urinary *N*-methylacetamide was evaluated as 16 hours (Borm et al., 1987). Half-lives of *N*-methylacetamide and *S*-(acetamidomethyl) mercapturic acid in 13 workers were estimated as 8.7 ± 1.9 and 29.4 ± 6.6 hours, respectively (Princivalle et al., 2010).

Several studies have also examined the pharmacokinetics of *N*,*N*-dimethylacetamide in children receiving an intravenous formulation of the DNA-alkylating drug busulfan, which uses *N*,*N*-dimethylacetamide as a vehicle (Oechtering et al., 2006; Hempel et al., 2007; Trame et al., 2013). The pharmacokinetics of *N*,*N*-dimethylacetamide in children could be described using a one-compartment model (Hempel et al., 2007; Trame et al., 2013) with a mean initial half-life of 3.74 hours, which decreased to 0.83 hours after 96 hours (Hempel et al., 2007). [The Working Group noted that these studies also had co-exposure to busulfan and other therapeutic agents.]

4.1.2 Experimental systems

Rats given *N*,*N*-dimethylacetamide excrete some of the same metabolites observed in humans. For example, rats exposed by subcutaneous injection to *N*,*N*-dimethylacetamide at 300 mg per day for 2 days excreted *N*-methylacetamide and acetamide in urine, suggesting that successive N-demethylation of *N*,*N*-dimethylacetamide occurs in rats (Barnes & Ranta, 1972). In rats, a single oral administration of ^{14}C-labelled *N*,*N*-dimethylacetamide resulted in metabolism to *N*-methylacetamide (60–70%), *N*-hydroxymethylacetamide (7–10%), and acetamide (7–10%) within 72 hours (EPA, 1995).

The plasma half-life of *N*,*N*-dimethylacetamide was between 0.6 and 1.5 hours in rats exposed by whole-body inhalation (Hundley et al., 1994). Half-lives of *N*-methylacetamide and *S*-(acetamidomethyl)mercapturic acid in urine were about 2.5 and 6.5 hours, respectively, in rats after exposure to *N*,*N*-dimethylacetamide at 200 mg/kg bw by gavage (Princivalle et al., 2010).

Incubation of liver microsomes from pyridine-induced rats with *N*,*N*-dimethylacetamide has shown that it is metabolized in vitro by cytochrome P450 (CYP), probably CYP2E1, to free radical metabolites that attack the haem prosthetic group, leading to enzyme inactivation (Tolando et al., 2001).

4.2 Mechanisms of carcinogenesis

This section summarizes the available evidence on the key characteristics of carcinogens (Smith et al., 2016), on whether *N*,*N*-dimethylacetamide: is genotoxic; induces oxidative stress; and alters cell proliferation, cell death, or nutrient supply.

N,*N*-Dimethylacetamide gave negative results in multiple test systems with respect to genotoxicity (see Table 4.1). For example, McGregor (1980) performed the following assays with *N*,*N*-dimethylacetamide: unscheduled DNA synthesis in human diploid fibroblasts (in vitro), tests for dominant lethal mutation in male rats and sperm morphology in male mice after exposure by inhalation, cytogenetic evaluations in male and female rat bone marrow after exposure by inhalation, and the sex-linked recessive lethal test in *Drosophila melanogaster* using atmospheric exposure. The results were negative for each of these assays. Terada et al. (1978) exposed mouse erythroleukaemia cells to *N*,*N*-dimethylacetamide, and inferred that DNA damage occurred based on changes in DNA sucrose sedimentation rates.

Acetamide, a metabolite of *N*,*N*-dimethylacetamide, has also been investigated for genotoxicity in several *D. melanogaster* assays with conflicting results (Mitchell et al., 1981; Valencia et al., 1985; Batiste-Alentorn et al., 1991, 1995; Muñoz & Barnett, 2003).

Other data relevant to the key characteristics of carcinogens were also available. Liu et al. (2016) found that *N*,*N*-dimethylacetamide increased reactive oxygen species (ROS) formation and decreased glutathione concentrations in cultured human hepatocytes at concentrations that were also associated with decreased cell viability and/or apoptosis. Apoptosis was the result of ROS-mediated activation of the TP53-BCL2 signalling pathway (Liu et al., 2016). *N*,*N*-Dimethylacetamide also promoted cell differentiation of several mammalian cell types in vitro (Tanaka et al., 1975; Ohta et al., 1976; Porter, 1979; Speers et al., 1979; Dutko & Oldstone, 1981; Andrews et al., 1986; Moore et al., 1986; Meng et al., 1995). Other studies in vitro have shown that *N*,*N*-dimethylacetamide can inhibit DNA synthesis in cultured human lymphocytes (Novogrodsky et al., 1980), and increase the cell proliferation of murine fibroblasts and protozoa (Sauvant et al., 1995).

4.3 Other adverse effects

4.3.1 Humans

Weiss et al. (1962) treated patients with metastatic tumours with *N*,*N*-dimethylacetamide by intravenous injection at up to 500 mg/kg bw per day for up to 5 consecutive days, and observed clinical chemistry changes consistent with hepatotoxicity and neurotoxicity. Occupational exposure to *N*,*N*-dimethylacetamide has also been associated with hepatotoxicity and effects on the central nervous system in workers (Corsi, 1971; Marino et al., 1994; Baum & Suruda, 1997; Su et al., 2000; Lee et al., 2006; Jung et al., 2007; see also the review by Kennedy, 2012). For example, two cases of hepatitis in women as a result of dermal exposure, in addition to "minor respiratory exposures", were reported among 25 workers exposed to *N*,*N*-dimethylacetamide in an acrylic-fibre production line (Baum & Suruda, 1997). Of 30 workers exposed to *N*,*N*-dimethylacetamide in the spinning department of an acrylic-polymer factory for 2–10 years, abnormalities in tests for liver function and hepatobiliary excretion were found in 19 cases (63%) (Corsi, 1971). Hepatic injuries were reported in 28 cases in 440 newly employed *N*,*N*-dimethylacetamide-exposed workers, with an observation period of 313.3 person-years, in two elastane-fibre plants. After controlling for confounders, urinary *N*-methylacetamide estimates of 20 or 30 mg/g creatinine were positively associated with hepatic injury with odds ratios of 3.70 (95% CI,

Table 4.1 Genetic and related effects of *N,N*-dimethylacetamide and its metabolite acetamide in in human cells in vitro and in experimental systems

Test system (species, strain, sex)	End-point	Results[a]		Agent, concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Human embryonic intestinal cells	Unscheduled DNA synthesis	–	(–)	*N,N*-Dimethylacetamide, 9366 µg/mL	The incorporation of radiolabel was insufficient to permit analysis of results in the presence of S9	McGregor (1980)
Rat, CD (M, F)	Chromosomal aberrations	–	NA	*N,N*-Dimethylacetamide, inhalation, 700 ppm, 7 h/d for 5 d		McGregor (1980)
Rat, CD (M)	Dominant lethal test	–	NA	*N,N*-Dimethylacetamide, inhalation, 700 ppm, 7 h/d for 5 d		McGregor (1980)
Rat, CD (M, F)	DNA damage	–	NA	*N,N*-Dimethylacetamide, inhalation, 700 ppm, 7 h/d for 5 d		McGregor (1980)
Mouse erythroleukaemia cell, strain 745A	DNA damage	+	NT	*N,N*-Dimethylacetamide, 30 mM		Terada et al. (1978)
Drosophila melanogaster	Sex-linked recessive lethal mutations	–	NA	*N,N*-Dimethylacetamide, 200 ppm, 95 min in atmosphere		McGregor (1980)
Drosophila melanogaster (sc z w sn)*	Somatic mutation and recombination test (SMART)	–	NA	Acetamide, 4500 ppm after feeding		Mitchell et al. (1981)
Drosophila melanogaster	Sex-linked recessive lethal mutations	–	NA	Acetamide, 50 000 ppm, after feeding or injection		Valencia et al. (1985)
Drosophila melanogaster, unstable Zeste–White (UZ)	SMART	+	NA	Acetamide, 10 mM	Doses tested: 0, 10, 20, and 30 mM; positive result at 10 mM	Batiste-Alentorn et al. (1991)
Drosophila melanogaster, trans-heterozygous (*mwh +/+flr*^{3})	SMART	+	NA	Acetamide, 50 mM	Doses tested: 0, 20, 30, and 50 mM; positive result at 50 mM	Batiste-Alentorn et al. (1995)

Table 4.1 (continued)

Test system (species, strain, sex)	End-point	Results[a]		Agent, concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Drosophila melanogaster	Chromosomal damage	+	NA	Acetamide, 0.5%, oral exposure	Doses tested: 0.5, 1, 1.5, 2, and 4%; females heterozygous for the genotype *y w f Df(1) n20/y w f Df(1)n49* were mated to males of the genotype *y Df(1)n23/B*^{S} *Y y*$^{+}$; decreased viability at ≥ 2%; nondisjunction may be due to toxicity	Muñoz & Barnett (2003)

d, day; F, female; HIC, highest ineffective concentration; LEC, lowest effective concentration; M, male; min, minute; NA, not applicable; NT, not tested; ppm, parts per million

[a] +, positive; –, negative; (–), negative in a study of limited quality

1.33–10.26) or 4.67 (95% CI, 1.66–13.15), respectively (Lee et al., 2006).

4.3.2 Experimental systems

Liver effects induced by short-term exposure to *N,N*-dimethylacetamide were consistently seen in mice (Malley et al., 1995; Valentine et al., 1997; JBRC, 2013a, b) and rats (Horn, 1961; Kinney et al., 1993; JBRC, 2013c, d).

Other tissues, including kidney, lymphoid organs, bone marrow, adrenal gland, and testis, were also affected in short-term studies in rodents (Horn, 1961; Valentine et al., 1997).

Non-neoplastic hepatic lesions seen in studies of chronic exposure by inhalation in mice and rats include centrilobular hepatocellular necrosis and hypertrophy. Hepatic cell proliferation was not seen in mice or rats after chronic exposure by inhalation. Other effects seen in rodents exposed to *N,N*-dimethylacetamide include chronic progressive nephropathy, renal papillary necrosis, and retinal atrophy (Malley et al., 1994; JBRC, 2013a, b, c, d).

4.4 Data relevant to comparisons across agents and end-points

See the monograph on 2-chloronitrobenzene in the present volume.

5. Summary of Data Reported

5.1 Exposure data

N,N-Dimethylacetamide is an amphiphilic chemical that is soluble in both water and organic solvents. It is a chemical with a high production volume, with global annual production estimated to be approximately 45 000 to 55 000 tonnes in 2000. The compound is used in the preparation of textile fibres, agrochemicals, pharmaceuticals, and fine chemicals. It is also used as a solvent for resins and in the manufacture of coatings and films.

N,N-Dimethylacetamide is not known to occur naturally, but it may be released to the environment during its production and downstream use, primarily as liquid effluent and gaseous emissions by venting.

The primary routes of exposure in human populations are inhalation and dermal uptake; dermal exposure is likely predominant in occupational settings, meaning that biomonitoring is preferred to air monitoring when estimating exposure.

Occupational exposures have been assessed in cross-sectional studies of workers in synthetic-fibre production facilities, using both air and biomonitoring methods. Occupational inhalation exposures were measured at a facility in the USA; workers involved in resin preparation and spinning operations were exposed to higher concentrations of *N*,*N*-dimethylacetamide than those involved in its manufacture. Some of these inhalation exposures were above the current occupational exposure limit. In a separate study (the only epidemiological study that was reviewed), a large number of air and urinary metabolite concentrations were measured in workers at an acrylic-fibre factory. Air concentrations of *N*,*N*-dimethylacetamide were generally low, although metabolites in urine were relatively high, indicating substantial uptake via the dermal route.

Low concentrations of *N*,*N*-dimethylacetamide have been measured in the plasma of children who were intravenously injected with a formulation of busulfan (an alkylating agent used in blood transfusion and bone-marrow transplantation) that contained *N*,*N*-dimethylacetamide as a solvent. Exposure to the compound in the general population from textile articles containing residual *N*,*N*-dimethylacetamide was reported to be negligible.

5.2 Cancer in humans

A small cohort study evaluating exposure to *N*,*N*-dimethylacetamide was conducted at a plant manufacturing acrylic fibre for hosiery, clothing, and upholstery in the Venice administrative region, Italy. The cohort included industrial workers employed for at least 1 year. Workers with past exposure to vinyl chloride or benzidine (classified as Group 1 by IARC, as causes of cancer of the liver and bladder, respectively) and administrative staff were excluded. Workers were grouped according to work area or job task, reflecting presumed differences in exposure levels, and into categories of duration of exposure and time since first exposure. Cancer mortality for the cohort was compared with the general regional population and found to be significantly elevated for cancers of the intestine and colon (4 cases, 0.38 expected), but the association between this elevation and exposure to *N*,*N*-dimethylacetamide was unclear. The study was limited by the young age of the cohort, leading to a low number of expected cancer deaths, and the relatively crude exposure assessment methodology.

5.3 Cancer in experimental animals

In the same laboratory, *N*,*N*-dimethylacetamide was tested for carcinogenicity in one well-conducted study that complied with good laboratory practice (GLP) in male and female mice exposed by inhalation, and in one well-conducted GLP study in male and female rats exposed by inhalation. *N*,*N*-Dimethylacetamide was tested in another laboratory in one study in male and female mice exposed by inhalation, and in one study in male and female rats exposed by inhalation. *N*,*N*-Dimethylacetamide was tested as a promoter in a limited initiation–promotion study by application to the cheek pouch of female Syrian golden hamsters.

In the GLP study in male mice, *N*,*N*-dimethylacetamide induced a significant positive trend in the incidence of and a significant increase in the incidence of hepatocellular adenoma.

In the GLP study in female mice, *N*,*N*-dimethylacetamide induced a significant positive trend in the incidence of and a significant increase

in the incidence of hepatocellular adenoma, of hepatocellular carcinoma, and of hepatocellular adenoma or carcinoma (combined).

In the other study in male and female mice, there was no significant increase in the incidence of any tumour.

In the GLP study in male rats, *N*,*N*-dimethylacetamide induced a significant positive trend in the incidence of hepatocellular adenoma, of hepatocellular carcinoma, and of hepatocellular adenoma or carcinoma (combined), and a significant increase in the incidence of hepatocellular adenoma and of hepatocellular adenoma or carcinoma (combined). The incidence of hepatocellular carcinoma in male rats exposed to the highest dose exceeded the upper bound of the range for historical controls.

In the GLP study in female rats, there was no significant increase in the incidence of any tumour.

In the other study in male and female rats, there was no significant increase in the incidence of any tumour.

In the study in hamsters, there was no increase in the incidence or multiplicity of any tumour.

5.4 Mechanistic and other relevant data

Information about the absorption, distribution, metabolism, and excretion of *N*,*N*-dimethylacetamide was derived from workers, human subjects, children undergoing chemotherapy, and experimental animals. *N*,*N*-Dimethylacetamide is absorbed from the skin, lung, and gastrointestinal tract. In humans, metabolites include acetamide. Rats excrete many of the same metabolites observed in humans.

Concerning the key characteristics of carcinogens, there is *weak* evidence that *N*,*N*-dimethylacetamide and its metabolite acetamide are genotoxic. No data in exposed humans were available. *N*,*N*-Dimethylacetamide gave negative results in tests for genotoxicity in human diploid fibroblasts, in rats exposed by inhalation (dominant lethal mutation test, bone marrow cytogenetics), and in *Drosophila melanogaster* (sex-linked recessive lethal test). In *D. melanogaster*, acetamide yielded conflicting results.

In vitro, *N*,*N*-dimethylacetamide promotes differentiation of several mammalian cell types, inhibits DNA synthesis in human lymphocytes, and increases cell proliferation in cultured murine fibroblasts and protozoa. There is *weak* evidence that *N*,*N*-dimethylacetamide alters cell proliferation, cell death, or nutrient supply.

Humans exposed to *N*,*N*-dimethylacetamide develop hepatotoxicity. In rats and mice, hepatotoxicity, including centrilobular hepatocellular necrosis and hypertrophy, was observed.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of *N*,*N*-dimethylacetamide.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of *N*,*N*-dimethylacetamide.

6.3 Overall evaluation

N,*N*-dimethylacetamide is *possibly carcinogenic to humans (Group 2B)*.

References

Andrews PW, Gönczöl E, Plotkin SA, Dignazio M, Oosterhuis JW (1986). Differentiation of TERA-2 human embryonal carcinoma cells into neurons and HCMV permissive cells. Induction by agents other than retinoic acid. *Differentiation*, 31(2):119–26. doi:10.1111/j.1432-0436.1986.tb00392.x PMID:3017799

Barnes JR, Ranta KE (1972). The metabolism of dimethylformamide and dimethylacetamide. *Toxicol Appl Pharmacol*, 23(2):271–6. doi:10.1016/0041-008X(72)90190-1 PMID:5074575

Batiste-Alentorn M, Xamena N, Creus A, Marcos R (1995). Genotoxic evaluation of ten carcinogens in the *Drosophila melanogaster* wing spot test. *Experientia*, 51(1):73–6. doi:10.1007/BF01964923 PMID:7843334

Batiste-Alentorn M, Xamena N, Creus A, Marcos R, Aaron CS (1991). Genotoxicity studies with the unstable zeste-white (UZ) system of *Drosophila melanogaster*: results with ten carcinogenic compounds. *Environ Mol Mutagen*, 18(2):120–5. doi:10.1002/em.2850180207 PMID:1908775

Baum SL, Suruda AJ (1997). Toxic hepatitis from dimethylacetamide. *Int J Occup Environ Health*, 3(1):1–4. doi:10.1179/oeh.1997.3.1.1 PMID:9891094

Borm PJ, de Jong L, Vliegen A (1987). Environmental and biological monitoring of workers occupationally exposed to dimethylacetamide. *J Occup Med*, 29(11):898–903. PMID:3681500

Cendana M, Lee S, Upadhyay PJ, Byrne JA, Shaw PJ, Earl J, et al. (2017). An HPLC-UV method for determining plasma dimethylacetamide concentrations in patients receiving intravenous busulfan. *Biomed Chromatogr*, 31(7):e3906. doi:10.1002/bmc.3906 PMID:27925250

ChemSpider (2015). *N,N*-Dimethylacetamide. Chemspider database. Search and share chemistry. Royal Society of Chemistry. Available from: http://www.chemspider.com/Chemical-Structure.29107.html?rid=da8567a5-cd8c-483b-b2ea-dea2bbbde503, accessed January 2020.

Corsi GC (1971). [On occupational pathology caused by dimethylacetmide (with special reference to hepatic function).] *Med Lav*, 62(1):28–42. [Italian] PMID:5095328

Dutko FJ, Oldstone MB (1981). Cytomegalovirus causes a latent infection in undifferentiated cells and is activated by induction of cell differentiation. *J Exp Med*, 154(5):1636–51. doi:10.1084/jem.154.5.1636 PMID:6271894

ECHA (2012). Draft background document for *N,N*-dimethylacetamide (DMAC). European Chemicals Agency Database. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu/, accessed January 2020.

EPA (1995). Metabolic fate of *N,N*-dimethyl-acetamide-carbonyl-14C in rats. Shrivastava SP, author. Prepared by Haskell Laboratory. Submitted to United States Environmental Protection Agency. Haskell Laboratory Report No. 686-74, dated 1974. NTIS/OTS0558322.

Gescher A, Threadgill MD (1990). *N,N*-Dimethylacetamide. In: Buhler DR, Reed DJ, editors. Ethel Browning's toxicity and metabolism of industrial solvents, 2nd ed., Vol 2: Nitrogen and phosphorus solvents. Elsevier Science Publishers BV.

Hempel G, Oechtering D, Lanvers-Kaminsky C, Klingebiel T, Vormoor J, Gruhn B, et al. (2007). Cytotoxicity of dimethylacetamide and pharmacokinetics in children receiving intravenous busulfan. *J Clin Oncol*, 25(13):1772–8. doi:10.1200/JCO.2006.08.8807 PMID:17470868

Honnert B, Grzebyk M (2010). Utilisation des amides en France. INRS – Hygiène et sécurité du travail. 219: 49-59 [French].

Horn HJ (1961). Toxicology of dimethylacetamide. *Toxicol Appl Pharmacol*, 3(1):12–24. doi:10.1016/0041-008X(61)90003-5 PMID:13715871

HSL (2018). *N,N′*-Dimethylacetamide monitored by analysis of *N*-methylacetamide (NMA) in urine. Biological monitoring guidance values. Buxton, England: Health & Safety Laboratory. Available from: https://www.hsl.gov.uk/media/1188365/n,%20n%E2%80%99%20-%20dimethylacetamide%20in%20urine.pdf, accessed January 2020.

Hundley SG, Lieder PH, Valentine R, McCooey KT, Kennedy GL Jr (1994). Dimethylacetamide pharmacokinetics following inhalation exposures to rats and mice. *Toxicol Lett*, 73(3):213–25. doi:10.1016/0378-4274(94)90061-2 PMID:8091430

IFA (2018). *N,N*-Dimethylacetamide. GESTIS International Limit Values database. Germany: Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (Institute for Occupational Safety and Health of the German Social Accident Insurance). Available from: https://www.dguv.de/ifa/gestis/gestis-internationale-grenzwerte-fuer-chemische-substanzen-limit-values-for-chemical-agents/index-2.jsp, accessed January 2020.

JBRC (2013a). Summary of inhalation carcinogenicity study of *N,N*-dimethylacetamide in B6D2F$_1$/Crlj mice [text]. 2013. Japan Bioassay Research Center. Available from: http://anzeninfo.mhlw.go.jp/user/anzen/kag/pdf/gan/0754_MAIN.pdf, accessed January 2020 [Japanese].

JBRC (2013b). Summary of inhalation carcinogenicity study of *N,N*-dimethylacetamide in B6D2F$_1$/Crlj mice [tables]. 2013. Japan Bioassay Research Center. Available from: http://anzeninfo.mhlw.go.jp/user/anzen/kag/pdf/gan/0754_TABLES.pdf, accessed January 2020.

JBRC (2013c). Summary of inhalation carcinogenicity study of *N,N*-dimethylacetamide in F344/DuCrlCrlj rat [text]. 2013. Japan Bioassay Research Center. Available from: http://anzeninfo.mhlw.go.jp/user/anzen/kag/pdf/gan/0753_MAIN.pdf, accessed January 2020 [Japanese].

JBRC (2013d). Summary of inhalation carcinogenicity study of *N,N*-dimethylacetamide in F344/DuCrlCrlj rat [tables]. Japan Bioassay Research Center. Available from: http://anzeninfo.mhlw.go.jp/user/anzen/kag/pdf/gan/0753_TABLES.pdf, accessed January 2020.

Jung SJ, Lee CY, Kim SA, Park KS, Ha BG, Kim J, et al. (2007). Dimethylacetamide-induced hepatic injuries among spandex fibre workers. *Clin Toxicol (Phila)*, 45(5):435–9. doi:10.1080/15563650601117897 PMID:17503240

Kawai T, Mizunuma K, Okada Y, Odachi T, Horiguchi S, Iguchi H, et al. (1997). Separate determination by gas chromatography of dimethylformamide, dimethylacetide, monomethylformamide and monomethylacetamide in urine for biological monitoring. *J Occup Health*, 39(2):113–8. doi:10.1539/joh.39.113

Kawata K, Ibaraki T, Tanabe A, Yagoh H, Shinoda A, Suzuki H, et al. (2001). Gas chromatographic-mass spectrometric determination of hydrophilic compounds in environmental water by solid-phase extraction with activated carbon fiber felt. *J Chromatogr A*, 911(1):75–83. doi:10.1016/S0021-9673(00)01252-8 PMID:11269598

Kennedy GL (2012). Toxicology of dimethyl and monomethyl derivatives of acetamide and formamide: a second update. *Crit Rev Toxicol*, 42(10):793–826. doi:10.3109/10408444.2012.725028 PMID:23013261

Kennedy GL Jr, Pruett JW (1989). Biologic monitoring for dimethylacetamide: measurement for 4 consecutive weeks in a workplace. *J Occup Med*, 31(1):47–50. PMID:2738751

Kinney LA, Burgess BA, Stula EF, Kennedy GL Jr (1993). Inhalation studies in rats exposed to dimethylacetamide (DMAc) from 3 to 12 hours per day. *Drug Chem Toxicol*, 16(2):175–94. doi:10.3109/01480549309031995 PMID:8486098

Lee CY, Jung SJ, Kim SA, Park KS, Ha BG (2006). Incidence of dimethylacetamide induced hepatic injury among new employees in a cohort of elastane fibre workers. *Occup Environ Med*, 63(10):688–93. doi:10.1136/oem.2005.023580 PMID:16728503

Liu X, Gong W, Xu YQ, Zhu BL (2016). Dimethylacetamide-induced hepatic Injury in vitro: mechanism and potential preventive strategy. *Biomed Environ Sci*, 29(2):153–7. PMID:27003174

Malley LA, Slone TW Jr, Makovec GT, Elliott GS, Kennedy GL Jr (1995). Chronic toxicity/oncogenicity of dimethylacetamide in rats and mice following inhalation exposure. *Fundam Appl Toxicol*, 28(1):80–93. doi:10.1006/faat.1995.1149 PMID:8566487

Malley LA, Slone TW Jr, Van Pelt C, Elliott GS, Ross PE, Stadler JC, et al. (1994). Chronic toxicity/oncogenicity of dimethylformamide in rats and mice following inhalation exposure. *Fundam Appl Toxicol*, 23(2):268–79. doi:10.1006/faat.1994.1105 PMID:7982535

Marino G, Anastopoulos H, Woolf AD (1994). Toxicity associated with severe inhalational and dermal exposure to dimethylacetamide and 1,2-ethanediamine. *J Occup Med*, 36(6):637–41. PMID:8071726

Mastrangelo G, Serena R, Marzia V (1993). Mortality from tumours in workers in an acrylic fibre factory. *Occup Med (Lond)*, 43(3):155–8. doi:10.1093/occmed/43.3.155 PMID:8400212

Maxfield ME, Barnes JR, Azar A, Trochimowicz HT (1975). Urinary excretion of metabolite following experimental human exposures to DMF or to DMAC. *J Occup Med*, 17(8):506–11. PMID:1234901

McGaughey C, Jensen JL (1980). Effects of the differentiating agents (inducers) dimethylacetamide, di- and tetramethylurea on epidermal tumor promotion by retinyl (vitamin A) acetate and croton oil in hamster cheek pouch. *Oncology*, 37(2):65–70. doi:10.1159/000225406 PMID:7360481

McGregor DF (1980). Tier II mutagenic screening of 13 NIOSH priority compounds, individual compound report, *N,N*-dimethyl-acetamide, Report No. 27. Cincinnati (OH), USA: National Institute of Occupational Safety and Health.

Meng X, Franquemont D, Speers WC (1995). Differentiation of murine embryonal carcinoma in vitro and in vivo with *N,N*-dimethyl acetamide. *Pathology*, 27(4):339–43. doi:10.1080/00313029500169263 PMID:8771152

Mitchell ID, Gilbert PJ, Brice AJ, White DJ (1981). Somatic eye mutation in *Drosophila melanogaster* as a short-term test for mutagens and carcinogens. *Carcinogenesis*, 2(8):783–6. doi:10.1093/carcin/2.8.783 PMID:6793259

Moore EE, Mitra NS, Moritz EA (1986). Differentiation of F9 embryonal carcinoma cells. Differences in the effects of retinoic acid, 5-bromodeoxyuridine, and *N′-N′*-dimethylacetamide. *Differentiation*, 31(3):183–90. doi:10.1111/j.1432-0436.1986.tb00399.x PMID:3021554

Muñoz ER, Barnett BM (2003). Chromosome malsegregation induced by the rodent carcinogens acetamide, pyridine and diethanolamine in *Drosophila melanogaster* females. *Mutat Res*, 539(1-2):137–44. doi:10.1016/S1383-5718(03)00158-X PMID:12948822

NIOSH (1994). Dimethyl acetamide Method 2004. NIOSH manual of analytical methods, 4th Edition. Cincinnati (OH), USA: National Institute for Occupational Safety and Health.

NIOSH (2016). NIOSH pocket guide to chemical hazards. Cincinnati (OH), USA: National Institute for Occupational Safety and Health.

Nomiyama T, Omae K, Ishizuka C, Yamauchi T, Kawasumi Y, Yamada K, et al. (2000). Dermal absorption of *N,N*-dimethylacetamide in human volunteers. *Int Arch Occup Environ Health*, 73(2):121–6. doi:10.1007/s004200050017 PMID:10741510

Novogrodsky A, Rubin AL, Stenzel KH (1980). A new class of inhibitors of lymphocyte mitogenesis: agents that induce erythroid differentiation in Friend leukemia cells. *J Immunol*, 124(4):1892–7. PMID:7189200

OECD (2009). The 2007 OECD list of high production volume chemicals. No. 112. Paris, France: Organisation for Economic Co-operation and Development. Available from: http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm, accessed January 2020.

OECD-SIDS (2001). *N,N*-Dimethylacetamide SIDS Initial Assessment Report for 13th SIAM (Bern, Switzerland, 6–9 November 2001). Available from: https://hpvchemicals.oecd.org/ui/handler.axd?id=16564422-daff-4489-8c27-735d3ab0b260, accessed January 2020.

OECD-SIDS (2012). SIDS Initial Assessment Profiles agreed in the course of the OECD HPV Chemicals Programme from 1993-2011. Health and Safety Publications. Series on Testing and Assessment No. 166. Inter-Organization Programme for the Sound Management of Chemicals. Paris, France: Organisation for Economic Cooperation and Development. Available from: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2012)4/part3&doclanguage=en, accessed January 2020.

Oechtering D, Boos J, Hempel G (2006). Monitoring of *N,N*-dimethylacetamide in children during i.v.-busulfan therapy by liquid chromatography-mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci*, 838(2):129–34. doi:10.1016/j.jchromb.2006.04.034 PMID:16725388

Ohta Y, Tanaka M, Terada M, Miller OJ, Bank A, Marks P, et al. (1976). Erythroid cell differentiation: murine erythroleukemia cell variant with unique pattern of induction by polar compounds. *Proc Natl Acad Sci USA*, 73(4):1232–6. doi:10.1073/pnas.73.4.1232 PMID:177980

Okuda H, Takeuchi T, Senoh H, Arito H, Nagano K, Yamamoto S, et al. (2006). Developmental toxicity induced by inhalation exposure of pregnant rats to *N,N*-dimethylacetamide. *J Occup Health*, 48(3):154–60. doi:10.1539/joh.48.154 PMID:16788275

Perbellini L, Princivalle A, Caivano M, Montagnani R (2003). Biological monitoring of occupational exposure to *N,N*-dimethylacetamide with identification of a new metabolite. *Occup Environ Med*, 60(10):746–51. doi:10.1136/oem.60.10.746 PMID:14504362

Porter PN (1979). Effects of murine erythroleukemia inducers on mouse erythroid colony formation in culture. *Differentiation*, 15(1):57–60. doi:10.1111/j.1432-0436.1979.tb01034.x PMID:294404

Princivalle A, Pasini F, Perbellini L (2010). *S*-(acetamidomethyl)mercapturic acid (AMMA): a new biomarker for occupational exposure to *N,N*-dimethylacetamide. *J Chromatogr B Analyt Technol Biomed Life Sci*, 878(27):2515–9. doi:10.1016/j.jchromb.2010.04.022 PMID:20462811

PubChem (2019). N,N-Dimethylacetamide. PubChem database. Bethesda (MD), USA: United States National Library of Medicine, National Center for Biotechnology Information. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/31374, accessed January 2020.

Sauvant MP, Pépin D, Grolière CA, Bohatier J (1995). Effects of organic and inorganic substances on the cell proliferation of L-929 fibroblasts and *Tetrahymena pyriformis* GL protozoa used for toxicological bioassays. *Bull Environ Contam Toxicol*, 55(2):171–8. doi:10.1007/BF00203006 PMID:7579920

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect*, 124(6):713–21. doi:10.1289/ehp.1509912 PMID:26600562

Speers WC, Birdwell CR, Dixon FJ (1979). Chemically induced bidirectional differentiation of embryonal carcinoma cells in vitro. *Am J Pathol*, 97(3):563–84. PMID:507191

Spies GJ, Rhyne RH Jr, Evans RA, Wetzel KE, Ragland DT, Turney HG, et al. (1995a). Monitoring acrylic fiber workers for liver toxicity and exposure to dimethylacetamide. 1. Assessing exposure to dimethylacetamide by air and biological monitoring. *J Occup Environ Med*, 37(9):1093–101. doi:10.1097/00043764-199509000-00010 PMID:8528717

Spies GJ, Rhyne RH Jr, Evans RA, Wetzel KE, Ragland DT, Turney HG, et al. (1995b). Monitoring acrylic fiber workers for liver toxicity and exposure to dimethylacetamide. 2. Serum clinical chemistry results of dimethylacetamide-exposed workers. *J Occup Environ Med*, 37(9):1102–7. doi:10.1097/00043764-199509000-00011 PMID:8528718

Su TC, Lin PH, Chiu MJ, Chu TS, Chang MJW, Wang JD, et al. (2000). Dimethylacetamide, ethylenediamine, and diphenylmethane diisocyanate poisoning manifest as acute psychosis and pulmonary edema: treatment with hemoperfusion. *J Toxicol Clin Toxicol*, 38(4):429–33. doi:10.1081/CLT-100100953 PMID:10930060

Tanaka M, Levy J, Terada M, Breslow R, Rifkind RA, Marks PA (1975). Induction of erythroid differentiation in murine virus infected eythroleukemia cells by highly polar compounds. *Proc Natl Acad Sci USA*, 72(3):1003–6. doi:10.1073/pnas.72.3.1003 PMID:165480

Tanaka S, Nomiyama T, Miyauchi H, Nakazawa M, Yamauchi T, Yamada K, et al. (2002). Monitoring for *N,N*-dimethylformamide and *N,N*-dimethylacetamide with a diffusive sampler using distilled water as

an absorbent. *AIHA J (Fairfax, Va)*, 63(6):726–31. doi:10.1080/15428110208984762 PMID:12570081

Terada M, Nudel U, Fibach E, Rifkind RA, Marks PA (1978). Changes in DNA associated with induction of erythroid differentiation by dimethyl sulfoxide in murine erythroleukemia cells. *Cancer Res*, 38(3):835–40. PMID:272229

ThermoFisher Scientific (2018). Safety data sheet: *N,N*-dimethylacetamide (revision 3). Available from: https://www.fishersci.com/store/msds?partNumber=D1601&productDescription=N%2CN-DIMETHYLACETAMIDE+GC+HS+1L&vendorId=VN00033897&countryCode=US&language=en, accessed January 2020.

Tolando R, Zanovello A, Ferrara R, Iley JN, Manno M (2001). Inactivation of rat liver cytochrome P450 (P450) by *N,N*-dimethylformamide and *N,N*-dimethylacetamide. *Toxicol Lett*, 124(1-3):101–11. doi:10.1016/S0378-4274(01)00384-8 PMID:11684362

Trame MN, Bartelink IH, Boos J, Boelens JJ, Hempel G (2013). Population pharmacokinetics of dimethylacetamide in children during standard and once-daily IV busulfan administration. *Cancer Chemother Pharmacol*, 72(5):1149–55. doi:10.1007/s00280-013-2284-9 PMID:24036908

Valencia R, Mason JM, Woodruff RC, Zimmering S (1985). Chemical mutagenesis testing in Drosophila. III. Results of 48 coded compounds tested for the National Toxicology Program. *Environ Mutagen*, 7(3):325–48. doi:10.1002/em.2860070309 PMID:3930234

Valentine R, Hurtt ME, Frame SR, Kennedy GL (1997). Inhalation toxicology of dimethylacetamide (DMAC) in mice and rats: agerelated effects on lethality and testicular injury. *Inhal Toxicol*, 9(2):141–56. doi:10.1080/089583797198321

Weiss AJ, Jackson LG, Carabasi RA, Mancall EL, White JC (1962). A phase I study of dimethylacetamide. *Cancer Chemother Rep*, 16:477–85. PMID:14005853

Yamamoto S, Matsumoto A, Yui Y, Miyazaki S, Kumagai S, Hori H, et al. (2018). Concentration determination of urinary metabolites of *N,N*-dimethylacetamide by high-performance liquid chromatography-tandem mass spectrometry. *J Occup Health*, 60(2):140–7. doi:10.1539/joh.17-0098-OA PMID:29213009