N-Isopropylaniline

(CAS No: 768-52-5)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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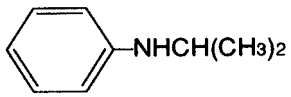
1 Introduction

The present document contains the assessment of the health hazard of *N*-isopropylaniline by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by MA Maclaine Pont, M.Sc. (Wageningen University and Research Centre, Wageningen, the Netherlands).

In May 2000, literature was searched in the databases Toxline, Medline, and Chemical Abstracts, starting from 1981, 1966, and 1937, respectively, and using the following key words: *N*-isopropylaniline; benzenamine, *N*-(1-methylethyl)-; and 768-52-5. The final search was carried out in Toxline and Medline in January 2003.

In April 2003, the President of the Health Council released a draft of the document for public review. The committee received no comments.

2 Identity

name	:	*N*-isopropylaniline
synonyms	:	benzenamine, *N*-(1-methylethyl)-; *N*-phenylisopropylamine
molecular formula	:	$C_9H_{13}N$
structural formula	:	
CAS number	:	768-52-5

Data from ACG99, NLM01.

3 Physical and chemical properties

molecular weight	:	135.21
boiling point	:	203°C; 206-208°C
melting point	:	approximately -50°C
flash point	:	100°C (open cup)
vapour pressure	:	at 25°C: 4 Pa
solubility in water	:	insoluble
log $P_{octanol/water}$	:	2.53 (estimated)
conversion factors	:	at 20°C, 101.3 kPa: 1 mg/m^3 = 0.18 ppm 1 ppm = 6.5 mg/m^3

Data from: ACG99, Lew00, Lid99, http://esc.syrres.com.

N-Isopropylaniline is a clear, straw-coloured liquid with a sweet, aromatic odour (ACG99).

When heated to decomposition, the compound emits toxic fumes of NO_X.

4 Uses

N-isopropylaniline is employed in the dyeing of acrylic fibres and as a chemical intermediate (ACG99).

5 Biotransformation and kinetics

After a single intraperitoneal injection of ^{14}C-*N*-isopropylaniline in male rats (Sprague-Dawley; n=6) at 15 mg/kg bw, approximately 70% of the radioactivity was excreted via the urine in the first 24 hours. 4-Hydroxy-*N*-isopropylaniline, *p*-aminophenol, and *N*-phenyl-2-aminopropionic acid were the only metabolites detected accounting for 61, 8, and less than 1% of the radioactivity, respectively. After 96 hours, 80-90% of the radioactivity was excreted via the urine. The rest of the radioactivity was not accounted for (Ale69).

6 Effects and mechanism of action

Human data

The committee did not find data on the toxic effects of *N*-isopropylaniline in humans.

Animal data

Irritation and sensitisation

N-isopropylaniline was stated to be slightly irritating to the eyes of rabbits. Except for minor irritation, eyes were clear by the third day, while all animals were free of irritation within 7 days (no more data presented) (Mon85).

N-isopropylaniline was stated to be slightly irritating to the skin of rabbits. All animals were free of irritation within 7 days (no more data presented) (Mon85).

In a range-finding study preceding a dermal sensitisation test, covered 6-hour application of 0.3 mL of undiluted and diluted (10, 25, 50%) *N*-isopropylaniline to the clipped skin of guinea pigs (Hartley albino) did not cause irritation (observation times: 24 and 48 hours). In the sensitisation test, application of undiluted material, once a week for 3 weeks, produced slight to moderate irritation and necrosis after the first and second induction, respectively, while there was no irritation at a new site after the third induction. Challenging 14 days after the last induction exposure did not cause a significant dermal response, but some minor dermal effects were seen in irritation-control animals. The results from this study suggest some possible (cumulative) irritation, but no sensitisation (Aul86).

Single exposure

Exposure of rats (Sprague-Dawley; n=5/sex/group) to analytical vapour/aerosol concentrations of *N*-isopropylaniline of 1400, 1400, 1300, and 1000 mg/m^3 *, for 4 hours, caused mortality, mostly within 2 days, in 9/10 (5 males, 4 females), 9/10 (5 males, 4 females), 5/10 (4 males, 1 female), and 1/10 (1 male) animals,

* Particle-size analysis showed mass median aerodynamic diameters (± geometric standard deviation) of ca. 1.1 ± 2.7, 1.7 ± 2.9, 1.2 ± 2.4, and 1.5 ± 2.3 µm, respectively.

respectively (observation period: 14 days). Apart from death, the most common signs of toxicity during inhalation were hypoactivity and breathing difficulties. Post-exposure observations included hypoactivity and weight loss in all survivors except those exposed to 1000 mg/m^3 that did not show signs of toxicity. No unusual gross necropsy findings were noted. From these data, a 4-hour LC_{50} of 1223 mg/m^3 was calculated (males: 1118 mg/m^3; females: 1349 mg/m^3) (Dud86).

For rabbits, a dermal LD_{50} of 3550 mg/kg bw has been listed (Mon85).

For rats, an oral LD_{50} of 560 mg/kg bw has been presented (Mon85).

In a range-finding micronucleus test, intraperitoneal LD_{50} values of 389, 693, and 547 mg/kg bw were calculated for male mice, female mice, and both sexes combined, respectively (CD-1; n=2-3/sex/dose; dose range: 245-3500 mg/kg bw) (Flo90).

Repeated exposure

Groups of 15 male and 15 female Sprague-Dawley rats were exposed to *N*-isopropylaniline vapour concentrations of 0, 0.31, 2.8, or 31 mg/m^3, 6 hours/day, 5 days/week, for 2 weeks. All animals survived the exposures. There were no abnormalities noted during exposure. Twenty-four hours after the last exposure, changes in haematology parameters and differences in carboxyhaemoglobin (CO-Hb) and methaemoglobin (Met-Hb) levels were observed between exposed and control animals (see Table 1). There were no treatment-related changes in absolute or relative organ weights, gross or microscopic pathology (Dud90).

Table 1 Treatment-related effects in Sprague-Dawley rats after inhalation exposure to *N*-isopropylaniline vapours, 6 hours/day, 5 days/week, for 2 weeks (Dud90).

	males (n=15)				females (n=15)			
	0 mg/m^3	0.31 mg/m^3	2.8 mg/m^3	31 mg/m^3	0 mg/m^3	0.31 mg/m^3	2.8 mg/m^3	31 mg/m^3
MCH[a] (pg)	19.99	20.21	19.97	20.17	19.89	20.74	20.78	22.11**
MCHC(g/dL)	32.69	32.91	32.75	32.85	33.17	34.78	35.25	37.27**
% CO-Hb	1.7	2.0*	1.6	1.33**	1.7	2.0*	1.7	1.2**
% Met-Hb	0.5	0.5	0.7	1.4**	0.6	0.4	0.7	1.5**

[a] MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration; CO-Hb = carboxyhaemoglobin; Met-Hb = methaemoglobin.
* $p<0.05$; ** $p<0.01$.

In concordance with the Dutch Expert Committee on Occupational Standards (DECOS), another committee of the Health Council of the Netherlands (DEC92), the committee considers CO-Hb levels ≤5% not to be toxicologically relevant, i.e., there will be only a small or negligible risk of effects on behaviour and mental capacities at these levels. Based on an increased Met-Hb level at 31 mg/m^3, the committee concludes that 2.8 mg/m^3 is an NOAEL for male and female rats after 2-week, intermittent inhalation exposure to *N*-isopropylaniline.

In rats (Sprague-Dawley; n=15/sex/group) exposed to analytical concentrations of *N*-isopropylamine of 0, 55, 160, or 490 mg/m^3, 6 hours/day, 5 days/week, for a total of 21 exposure days, clinical signs observed during the exposure periods included salivation, lachrymation, and hypoactivity in the high-concentration group, and dose-related increases in the frequency of nasal and oral discharge and encrustation, especially in the 2 higher concentration groups. Body weights of the animals exposed to 490 mg/m^3 were statistically significantly lower than those of controls throughout the study. Analyses of blood samples collected from 10 animals/sex/group on study day 16 and from all animals just prior to termination (study days 29-31) showed statistically significantly elevated Met-Hb levels at all exposure concentrations at both time points. In the low- and mid-concentration groups, they amounted to ca. 2.7% and 4.4%, respectively, at both time points, while levels in the high-concentration groups rose from 6.3% to 9.5%. Changes in other blood values indicated a mild haemolytic response in all exposure groups. Further, increases in total bilirubin and serum alanine aminotransferase (ALAT) levels were seen in the high-concentration animals. Organ weight changes included increases in relative spleen and kidney weights of males and females of the mid- and high-concentration groups, in absolute spleen weights of males and females of the high-concentration group and in males of the mid-concentration group, and in relative liver weights in high-concentration females. Upon macroscopic and microscopic examination, there were spleen (enlarged and/or purple-coloured primarily in high-concentration animals; congestion, increased haematopoiesis) and kidney (random cortical nephrosis with regeneration ranging to nephropathy in males; nephrosis with regeneration in the pars recta in females) lesions in nearly all animals exposed to 160 or 490 mg/m^3. In the group exposed to 5 mg/m^3, 4 females showed increased haematopoiesis while renal lesions were observed in males. Based on reduced Hb and increased Met-Hb levels and increased splenic haematopoiesis, 55 mg/m^3, the lowest level tested, was the LOAEL in this study (Rol85).

Groups of 15 male and 15 female Sprague-Dawley rats were exposed to *N*-isopropylaniline concentrations of 0, 5, 20, or 100 mg/m^3, 6 hours/day, 5 days/

week, for approximately 14 weeks. The particle size was not analysed due to low aerosol concentrations of the exposure atmospheres. The treatment-related effects are summarised in Table 2. The authors concluded the following. Ophthalmologic examination of the control and high-level animals showed no ocular changes that could be attributed to test material exposure.

Table 2 Treatment-related effects in Sprague-Dawley rats after inhalation exposure to *N*-isopropylaniline, 6 hours/day, 5 days/ week, for approximately 14 weeks (Bec88).

	males (n=15)				females (n=15)			
	0	5	20	100 mg/m^3	0	5	20	100 mg/
HGB[a] (g/dL)	16.0	16.1	15.6	15.3*[b]	16.0	16.1	15.9	15.0
MCV (femto-L)	55.0	55.5	55.4	58.3**[b]	56.7	59.6	59.7	61.6**
MCHC (g/dL)	35.4	35.4	35.6	35.5	35.4	34.9	33.9**	34.1*
relative spleen wt	0.165	0.167	0.165	0.162*	0.177	0.180	0.192	0.199
relative kidney wt	0.747	0.758	759	0.835*	0.674	0.717	0.725	0.773*
spleen:								
increased haematopoiesis[c]	2	1	4	2	0	2	4	6
increased haemosiderin[c]	0	0	0	15**	0	1	0	15**
% O_2-Hb	24.8	17.4	18.8	18.5	21.7	21.8	22.3	20.1
% CO-Hb	0.3	0.2	-0.1**	-0.8**	0.4	0.3	0.2	-0.5**
% Met-Hb	0.9	1.4**	1.9**	4.0**	0.9	1.4**	1.9**	3.5**

[a] HGB = haemoglobin level; MCV = mean corpuscular volume; MCHC = mean corpuscular haemoglobin concentration; O_2-Hb = oxyhaemoglobin; CO-Hb = carboxyhaemoglobin; Met-Hb = methaemoglobin.

[b] Within historical control range.
* $p<0.05$, ** $p<0.01$.

[c] Expressed as number of animals.

Methaemoglobinaemia, occurring in all exposure groups, was considered a treatment-related effect and displayed a definite dose response. The decreased haemoglobin values and increased MCV values appeared to be treatment-related but were within or very slightly above the historical control range, and, therefore, not considered to be relevant. The increase in both relative and absolute kidney weights in the high-level animals and the dark discolouration of the high-level male kidneys could be associated to test-material exposure. These changes were not accompanied by any obvious microscopic abnormalities and, therefore, their biological significance is unknown. Microscopically, increased haemosiderin in the spleens of all the high-level animals was considered a treatment-related effect and may have contributed to the slight increase in splenic weight for this group.

The increase in haemosiderin pigment in concert with some changes in haematology suggested that there might have been some alteration in red blood cell kinetics leading to accelerated red blood cell destruction. The mild increase in absolute spleen weight for mid-level females was not accompanied by any obvious microscopic abnormality and, therefore, was probably of no biological or toxicological significance. All other microscopic changes were considered non-exposure related (Bec88).

With respect to this 14-week inhalation study, the committee concludes that 5 mg/m^3, the lowest concentration tested, was a LOAEL inducing methaemoglobinaemia in male and female rats.

Groups of 10 male and 10 female Sprague-Dawley rats received dermal doses of *N*-isopropylaniline of 0, 25, 100, or 400 mg/kg bw, 6 hours/day, 5 days/week, for approximately one month (see Table3). The compound was applied undiluted and left unoccluded on the shaved skin. Approximately one-third of the test material apparently volatilised. Haematology and blood chemistry parameters were evaluated for all animals at sacrifice. All animals were given a complete gross necropsy. Brain, heart, kidneys, liver, spleen, and testes with epididymides weights were recorded at scheduled sacrifice. Approximately 30 tissues per animal were preserved. All tissues from the control and high-dose animals were examined microscopically. Tissues from the low- and mid-dose groups were also examined if treatment-related effects were noted at the high-dose level.

Table 3 Treatment-related effects after dermal dosing of *N*-isopropylaniline to Sprague-Dawley rats during one month (Nay87).

	males (n=10)				females (n=10)			
	0	25	100	400 mg/kg	0	25	100	400 mg/kg
RBC[a] ($10^6/mm^3$)	7.00	7.96	7.83	7.15**	7.95	7.76	7.39**	7.04**
HGB (g/dL)	16.0	15.2**	15.0**	14.2**	15.7	15.1	14.5**	14.7*
MCV (femto-L)	67.3	50.2	57.7	61.0**	58.1	57.7	58.2	63.4**
MCH (pg)	20.2	19.1*	19.2	19.9	19.7	19.5	19.7	20.9**
MCHC (g/dL)	35.2	34.0	33.3**	32.6**	34.0	33.8	33.8	32.9**
reticulocytes (% of RBC)	1.00	1.30	2.10	3.16**	1.68	1.69	2.21	3.32**
relative spleen wt	0.190	0.196	0.200	0.256*	0.221	0.229	0.237	0.270*
spleen:								
increased haemosiderin[b]	0	0	0	10**	3	0	7	10**
increased haematopoiesis[b]	0	1	4	10**	1	3	3	8**

% O_2 -Hb	28.03	23.09	25.55	26.87	29.64	33.34	32.88	33.99
% CO-Hb[c]	0.56	0.54	-0.2	-1.27	0.49	0.69	0.32	0.05
% Met-Hb	1.15[BT]	1.42	2.78**	5.91**	1.06[BT]	1.31	2.07**	3.43**

[a] RBC = total erythrocyte count; HGB = haemoglobin level; MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration; O_2-Hb = oxyhaemoglobin; CO-Hb = carboxyhaemoglobin; Met-Hb = methaemoglobin.

[b] Expressed as number of animals.

[c] Elevated percentages of Met-Hb interfered with analysis of % CO-Hb in certain samples, causing apparent negative values to be reported; a statistical analysis was not performed and % desoxy-Hb could not be reliably determined.

[BT] Bartlett's test indicates statistically significant difference ($p<0.01$) among variances of the different groups.

* $p<0.05$, ** $p<0.01$.

Skin abnormalities (dryness, abrasions, redness and/or scab formation) were noted at all dose levels, but were most common in 100- and 400-mg/kg females. Some of the lesions, particularly those noted at the lower dose levels, may have resulted from periodic shaving of the application sites before exposure. The percentage oxyhaemoglobin (O_2-Hb), percentage carboxyhaemoglobin (CO-Hb), percentage methaemoglobin (Met-Hb), and percentage oxygen content of the blood were also determined. The deoxyhaemoglobin was also required by the protocol. However, due to interference in the measurement of CO-Hb in some animals with elevated Met-Hb levels, accurate results could not be reliably determined since the percentage deoxyhaemoglobin is determined from the total of % O_2-Hb, % CO-Hb, and % Met-Hb. The effect of this deviation from the protocol on the results of the study could not be ascertained. Anyway, the authors concluded the following. Anaemia and methaemoglobinaemia, with associated splenic changes of increased weight and haemosiderin deposition and haemosiderosis, were present at the mid- and/or high-dose levels in both sexes. Epidermal thickening (acanthosis) was seen at all dose levels in males and at the 2 highest doses in females. Based on the above results, *N*-isopropylaniline appeared to be absorbed through the intact skin of rats and produced a mild skin irritation and thickening as well as anaemia, methaemoglobinaemia, and associated splenic changes (Nay87). With respect to this 1-month dermal study, the committee concludes that 25 mg/kg bw, the lowest dose tested, is a LOAEL inducing an increase for the haemoglobin content of the blood of male rats, when administered dermally.

The committee did not find data on toxic (including carcinogenic) effects following long-term exposure to *N*-isopropylaniline.

Mutagenicity and genotoxicity

In vitro, *N*-isopropylaniline was negative in a gene mutation assay using *S. typhimurium* strains TA100, TA1535, and TA1537 with and without metabolic activating systems containing 10% induced rat or hamster liver S9. In strain TA98, results were negative when tested without (2 separate experiments) and with metabolic activation containing 5% or 30% induced hamster liver (one experiment each) or 10% rat liver S9 (2 separate experiments); in the presence of a 10% hamster liver S9-containing metabolic activation mix, a weakly positive (with 1.6-, 2,2-, and 2.2-fold increases in number of mutants over controls), a questionable positive (1.3-, 1.4-, and 1.7-fold increases), and a negative result were obtained (Zei87). *N*-isopropylaniline (purity: 97.4%) did not induce unscheduled DNA synthesis in primary rat hepatocyte cultures when tested in 2 separate experiments at adequate dose ranges (Bak86).

In vivo, a single intraperitoneal dose of 200 mg/kg bw did not cause a statistically significant increase in the number of micronucleated polychromatic erythrocytes (PCE) obtained from bone marrow of male and female mice (n=5/sex/group) sacrificed 24 or 48 hours after injection. This dose, selected from a rang-finding study (see section 'single exposure'), caused a statistically significant decrease in the PCE/total erythrocyte ratio in treated male mice sacrificed at 48 h, but not in any of the other *N*-isopropylaniline-treated or control groups. In the treated males sacrificed at 48 hours (but not in the other groups), mean body weights were statistically significantly decreased as well (Flo90).

Reproduction toxicity

Groups of 20 male Sprague-Dawley rats were exposed to (analytical) concentrations of *N*-isopropylaniline of 0, 5, 20, or 100 mg/m^3, 6 hours/day, 5 days/week, for approximately 11 weeks. Exposures continued on a 5-day-per-week schedule during a 2-week mating period, during which each male was co-housed with one untreated female for 5 nights, and 3 days later with a second untreated female for another 5 nights, and for 2 weeks thereafter. Males were then discarded without necropsy (except in case of unscheduled death). Females were sacrificed on gestational days 14 or 15, and uteri and ovaries were examined to assess pregnancy status, number and state of nidations and corpora lutea. No effects on body weight or clinical signs of toxicity were noted during the exposure period in any of the treated male groups. Treatment did not affect male fertility. In females, no effects were seen on copulation rates, pregnancy

rates, pre-coital times, or on the incidence of pre- and post-implantation losses and the number of dead fetuses (Rey88). From this study, the committee concluded that the NOAEL for male rat fertility following inhalation exposure is ≥100 mg/m^3.

Groups of 25 female Sprague-Dawley rats were exposed to (analytical) concentrations of 0, 5, 20, or 100 mg/m^3, 6 hours/day, 5 days/week, for approximately 11 weeks. Exposures continued on a 5-day-per-week schedule during the mating period during which each female was co-housed with one untreated male for 5 days or, in case of no mating/copulatory evidence, 3 days later with another untreated male for another 5 days. Once copulation was confirmed, females were exposed on a 7-day-per-week basis during gestational days 0 through 20. They were allowed to deliver their pups. On lactation day 4, litters were culled randomly to 8 pups, 4 of each sex, when possible. All adult females with litters were necropsied after weaning, all weanling pups on approximately lactation day 21. No clinical signs of toxicity of compound-related changes in survival, body weight (gain), and gross pathology were seen in any of the maternal animal groups; haematology, organ weight determination, and microscopic examination were (obviously) not performed in the maternal animals. In the high-exposure group, there were fewer confirmed copulations (20 vs. 24). In this group, pregnancy rate was decreased: pregnant females included 48% of the paired females and 60% of females with confirmed copulation (compared to 72 and 75%, respectively, among controls). The cause of the decrease in pregnancy rate was not determined. Pre-coital and gestational time lengths were not affected. With respect to the offspring, there were no changes in litter size, pup viability, pup weights, gross lesions, or microscopic observations (examined only in high concentration group) in any of the treated weanling groups (Rey88). From this study, the committee concluded that the NOAELs for maternal, female fertility, and developmental toxicity in rats following inhalation exposure are ≥100, 20, and ≥100 mg/m^3, respectively.

In a range-finding oral (gavage) study, female Charles River COBS CD rats (n=5/group) received daily doses of *N*-isopropylaniline of 0, 5, 25, 75, 150, or 300 mg/kg bw on gestational days 6 through 15, and were sacrificed at gestational day 20. Maternal toxicity observed included decreased mean body weight gains during treatment and throughout the entire gestation period in the 300-mg/kg bw group and enlarged, discoloured spleens in the 150- and 300-mg/kg bw groups. Developmental toxicity was found in the 300-mg/kg bw group only and consisted of decreases in the mean number of viable fetuses and in the mean total implantations and an increase in the mean post-implantation loss (Sku84). In the subsequent study, mated female rats (n=25/group) received

daily doses of 0, 30, 100, or 350 mg/kg bw on gestational days 6 through 15. The study was terminated by scheduled sacrifice of the dams on gestational day 20, which was immediately followed by Caesarean sections to examine uteri and ovaries and to remove fetuses for evaluation. In the high-dose group, 2 dams died. Further, maternal toxicity was observed in the form of excessive salivation, hair loss, decreased activity and/or brown urine, and decreased body weight gain. A dose-related increase in the occurrence of a dark and/or enlarged spleen was observed in dams of the mid- and high-dose groups. Increased extramedullary haematopoiesis was noted at microscopic examination of a random sample of 4 high-dose dams. Similar gross findings suggested the presence of this microscopic finding in the mid- and high-dose dams not microscopically examined. There were no biologically meaningful differences in maternal survival, appearance, behaviour, or body weight gain between the low- and mid-dose group dams and the controls. In the high-dose group, statistically significant increases in post-implantation loss and the number of dead fetuses, a statistically significant decrease in fetal weight, a statistically significant increase in the number of litters with malformed fetuses (primarily bent ribs, bent scapulae, and bent limb bones; brachymelia, brachydactyly, anasarca, and bent clavicle were seen as well), and an increase in the incidence of number of fetuses with skeletal variations. In the low- and mid-dose groups, Caesarean section observations, or fetal morphological findings were comparable to those in the control group (Lau84). From this study, the committee concludes that the NOAELs for maternal and developmental toxicity in rats following oral exposure are 30 and 100 mg/kg bw/day, respectively.

7 Existing guidelines

The current occupational exposure limit (MAC) for *N*-isopropylaniline in the Netherlands is 10 mg/m^3 (2 ppm), 8-hour TWA, with a skin notation.

Existing occupational exposure limits for *N*-isopropylaniline in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

The committee did not find data on the toxicokinetics and toxicodynamics of *N*-isopropylaniline in humans.

Following a single intraperitoneal injection into rats, 70 and 80-90% of the radioactivity administered were excreted in the urine after 24 and 96 hours,

respectively, 4-hydroxy-*N*-isopropylaniline being the main metabolite, while no parent compound was detected.

N-isopropylaniline was stated to be slightly irritating to the eyes and skin of rabbits. In guinea pigs, there were indications of some slight (cumulative) irritation but not of a sensitising potential.

Acute lethal toxicity data included a 4-hour LC_{50} of 1223 mg/m^3 in rats and a dermal LD_{50} of 3550 mg/kg bw in rabbits.

From 2- and 14-week inhalation and 4-week dermal toxicity studies, the committee concludes that methaemoglobinaemia is the main effect following repeated exposure to *N*-isopropylaniline in rats. In the 14-week study (Bec88), a statistically significant, dose-dependent increase in the percentage of Met-Hb was found in rats, ranging from 1.4 to 3.5-4% at 5 and 100 mg/m^3, the lowest and highest concentrations tested, respectively. At the latter level, effects on kidneys (increased weights; dark discolouration in males) and spleens (increased weights; increased haemosiderin pigment) were observed as well.

The fertility of male rats was not affected when exposed to 100 mg/m^3 for 11 weeks before mating with untreated females. In females exposed to 100 mg/m^3 for 11 weeks before mating with untreated males, pregnancy rate was decreased, but there were no effects on pregnancy outcome. Female fertility was not affected at exposure to 20 mg/m^3. When female rats were orally treated during gestational days 6 to 15, no developmental effects and slight maternal toxicity (dark and/or enlarged spleens) were seen at doses of 100 mg/kg bw. Doses of 350 mg/kg bw induced developmental effects (increased post-implantation losses, increased number of dead fetusus, decreased fetal weights, increased number of litters with malformed fetuses, increased number of fetuses with skeletal malformations) as well as maternal toxicity (mortality, excessive salivation, hair loss, decreased activity, brown urine, decreased body weight gain, enlarged/dark spleen, increased extramedullary haematopoiesis).

N-isopropylaniline was not mutagenic in *S. typhimurium*. It did not cause DNA damage (UDS) in cultured rat hepatocytes. *In vivo*, it did not induce increases in the frequency of micronuclei in bone marrow of intraperitoneal injected mice. The committee did not find data on the potential carcinogenicity of *N*-isopropylaniline.

The committee considers methaemoglobinaemia to be the critical effect, and the 14-week inhalation study with rats (Bec88) as the key study. At the lowest concentration tested, 5 mg/m^3, the percentage of Met-Hb was increased. However, this was only a marginal increase, also when taken into account that a similar percentage of Met-Hb (viz., 1.4%) was found after exposure to 31 mg/m^3 for 2 weeks (Table 1). Both figures were statistically significantly increased

compared with the control groups; however, the biological significance of this increase is questionable. Furthermore, the ACGIH has a Biological Exposure Index of 1.5% MetHb. Therefore, the committee considers 5 mg/m^3 as a NOAEL that can be taken as a starting point in deriving a health-based recommended occupational exposure limit (HBROEL). For extrapolation to a HBROEL, an overall assessment factor of 9 is established. This factor covers the following aspects: inter- and intraspecies variation. Thus, applying this factor of 9 and the preferred-value approach, a health-based occupational exposure limit of 0.5 mg/m^3 is recommended for *N*-isopropylaniline.

The committee recommends a health-based occupational exposure limit for *N*-isopropylaniline of 0.5 mg/m^3, as an 8-hour time-weighted average (TWA).

Because of lack of quantitative data on skin absorption, the committee cannot advise with respect to a skin notation.

References

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Annex

Occupational exposure limits for *N*-isopropylaniline in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	2	10	8 h	administrative	S	SZW03
Germany						
- AGS	-	10	8 h		S	TRG00
- DFG MAK-Kommission	-	-				DFG02
Great Britain						
- HSE	-	-				HSE02
Sweden	-	-				Swe00
Denmark	2	10	8 h		S	Arb02
USA						
- ACGIH	2	-	8 h	TLV	S	ACG03b
- OSHA	-	-				ACG03a
- NIOSH	2	10	10 h	REL	S	ACG03a
European Union						
- SCOEL	-	-				EC03

[a] S = skin notation, which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.