n-Butyl acrylate / butyl prop-2-enoate

MAK Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the workplace (MAK value) of 2 ml/m³ for n-butyl acrylate. The critical effect in a two-year inhalation study with rats was reserve cell hyperplasia with loss of ciliated or olfactory cells at the lowest concentration of 15 ml/m³. The lower confidence limit of the benchmark dose for an extra risk of 5% increase of the critical effect incidence ($BMDL_{05}$) of about 3 ml/m³, which had been calculated in the previous evaluations, was confirmed. Since 2014, the Commission uses an empirical approach to set MAK values for substances with critical effects on the upper respiratory tract or the eyes. Based on this approach, the equivalent concentration at the workplace is 1.5 ml/m³. However, studies in humans to investigate the sensory irritation of n-butyl acrylate are lacking. As the structurally related ethyl acrylate possesses a RD_{50} value as well as subchronic and chronic NOAECs similar to those of n-butyl acrylate, the NOAEC of 2.5 ml ethyl acrylate/m³ for sensory irritation in volunteers was used as a read-across. As the MAK value for ethyl acrylate has been set at 2 ml/m³, the MAK value of 2 ml/m³ for n-butyl acrylate could be confirmed. In analogy to ethyl acrylate, the assignment of n-butyl acrylate to Peak Limitation Category I and the excursion factor of 2 were confirmed. The NOAECs for developmental toxicity in rats and mice are sufficiently high so that damage to the embryo or foetus is unlikely when the MAK value is observed. Thus, n-butyl acrylate continues to be classified in Pregnancy Risk Group C. The substance is marginally clastogenic in vitro but not in vivo and was not carcinogenic in a 2-year inhalation study in rats. There are only a few cases of contact sensitization in humans but there are positive results in local lymph node assays. Data on airway sensitization are still not available. n-Butyl acrylate continues to be designated with "Sh". Skin absorption was calculated to contribute significantly to the systemic toxicity and n-butyl acrylate is designated with an "H".

Keywords

acrylic acid n-butyl ester; butyl acrylate; butyl propenate; butyl 2-propenoate; butyl prop-2-enoate; 2-propenoic acid butyl ester; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; allergenic effects; reproductive toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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n-Butyl acrylate

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Supplement 2017

MAK value (1996)	**2 ml/m³ (ppm) ≙ 11 mg/m³**
Peak limitation (2000)	**Category I, excursion factor 2**
Absorption through the skin (2016)	**H**
Sensitization (1985)	**Sh**
Carcinogenicity	**–**
Prenatal toxicity (2007)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
Solubility	1.7 g/l water (ECHA 2015 a)
log K_{OW}[1]	2.38 (ECHA 2015 a)
Vapour pressure at 22.2 °C	5 hPa (ECHA 2015 a)

Documentation was published in 1985 (documentation "n-Butyl acrylate" 1993), followed by supplements in 1996 (supplement "n-Butyl acrylate" 1999 (MAK value)), 1999 (supplement "n-Butyl acrylate" 2001 (allergenic effects)), 2000 (supplement "n-Butylacrylat" 2000 (peak limitation), available in German only) and 2007 (supplement "n-Butylacrylat" 2007 (prenatal toxicity), available in German only). The purpose of this supplement was to re-evaluate local irritation based on the proposals made by Brüning et al. (2014) and to review the benchmark concentrations calculated in the 1996 supplement (supplement "n-Butyl acrylate" 1999).

Mechanism of Action

In vitro studies showed that hydrolysis of the acrylate ester and the accompanying formation of acrylic acid is a detoxification mechanism. It is not the release of acid that is decisive for the toxicity of short-chain acrylates and methacrylates, but the reactivity of the Michael system (alpha-beta unsaturated compounds) with nucleo-

1) octanol/water partition coefficient

philic compounds such as glutathione (McCarthy and Witz 1997; McCarthy et al. 1994; Silver et al. 1981).

There are no great differences in the rate of hydrolysis of methyl acrylate, ethyl acrylate and *n*-butyl acrylate (Miller et al. 1981; Roos 2015).

Toxicokinetics and Metabolism

Ingested *n*-butyl acrylate is almost completely absorbed by rats (ECHA 2015 a).

Experimental data for dermal absorption are not available. With the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995), dermal fluxes of 4.094, 0.190 and 0.156 mg/cm^2 and hour, respectively, were obtained for a butyl acrylate concentration of 1.3%, which is the challenge concentration in the maximization test and thus regarded as not irritating to the skin (supplement "n-Butyl acrylate" 2001). This would correspond to the total absorption of 8188, 380 and 312 mg *n*-butyl acrylate, respectively, after the exposure of both hands and forearms (about 2000 cm^2) for 1 hour. After exposure to a saturated aqueous solution, 1070 mg, 50 mg and 41 mg are absorbed.

Effects in Humans

A number of earlier clinical findings with *n*-butyl acrylate, some of which, however, were incompletely documented, revealed skin-sensitizing effects of *n*-butyl acrylate in humans (supplement "n-Butyl acrylate" 2001). Only very few other case reports with positive patch test results (for example Shanmugam and Wilkinson 2012; Vogel et al. 2014) and some clinical epidemiological studies in small cohorts (for example Aalto-Korte et al. 2010; Christoffers et al. 2013; Ramos et al. 2014) have been published since the 1999 supplement (supplement "n-Butyl acrylate" 2001). These showed that the number of contact allergic reactions caused by *n*-butyl acrylate remains similar to that caused by ethyl acrylate. A 2+ reaction to *n*-butyl acrylate was observed in 2 of 24 patients with sensitization to epoxy (meth)acrylates; the patients also reacted to numerous other acrylates or methacrylates (Aalto-Korte et al. 2009).

No findings are available for sensitizing effects on the respiratory tract.

There are no recent data available for any other end points.

Animal Experiments and in vitro Studies

Acute toxicity

Inhalation

The RD_{50} for *n*-butyl acrylate in mice is 340 ml/m^3 (ECHA 2015 a) and thus almost equal to the RD_{50} of 315 ml/m^3 determined for ethyl acrylate (ECHA 2015 b).

Table 1 Nasal findings in the 2-year study in Sprague Dawley rats (BASF 1985 in supplement "n-Butyl acrylate" 1999)

		Number of males with findings				Number of females with findings			
Findings	Time (months)	0 ml/m³	15 ml/m³	45 ml/m³	135 ml/m³	0 ml/m³	15 ml/m³	45 ml/m³	135 ml/m³
reserve cell hyperplasia[1)]	12	0/10	0/11	0/13	0/12	0/11	0/10	0/10	0/10
	18	0/16	0/18	1/15	0/18	0/17	0/20	1/16	0/19
	24	0/19	0/19	2/16	0/15	0/16	1/19	1/18	0/23
	24 + 6	0/41	1/36	17/40	3/40	0/41	0/36	2/42	7/33
	total	0/86	1/84	20/84**	3/85	0/85	1/85	4/86	7/85*
reserve cell hyperplasia[2)]	12	0/10	0/11	0/13	5/12	0/11	0/10	0/10	9/10
	18	0/16	0/18	8/15	18/18	0/17	0/20	3/16	18/19
	24	0/19	2/19	11/16	15/15	0/16	6/19	5/18	20/23
	24 + 6	0/41	0/36	10/40	16/40	0/41	0/36	4/42	4/33
	total	0/86	2/84	29/84**	54/85**	0/85	6/85*	12/86**	51/85**
atrophy	12	0/10	0/11	0/13	0/12	0/11	0/10	0/10	0/10
	18	0/16	4/18	0/15	0/18	0/17	0/20	3/16	0/19
	24	0/19	0/19	0/16	0/15	0/16	0/19	0/18	0/23
	24 + 6	0/41	6/36	13/40	16/40	1/41	1/36	2/42	2/33
	total	0/86	10/84**	13/84**	16/85**	1/85	1/85	5/86	2/85

[1)] without the loss of olfactory or ciliated cells
[2)] with the loss of olfactory or ciliated cells
* $p < 0.05$
** $p < 0.01$

Subacute, subchronic and chronic toxicity

Inhalation

The NOAEC (no observed adverse effect concentration) for effects on the nose was 21 ml/m³ for Sprague Dawley rats after 90-day inhalation exposure to 0, 21, 108, 211 or 546 ml/m³ (ECHA 2015 a). In contrast, the local 90-day NOAEC was 25 ml/m³ for ethyl acrylate in F344 rats after exposure to 0, 25, 75 or 225 ml/m³ (ECHA 2015 b).

The MAK value for *n*-butyl acrylate was derived from a 2-year study in Sprague Dawley rats; after exposure to 0, 15, 45 or 135 ml/m³, even the low concentration of 15 ml/m³ led to hyperplasia and atrophy of the olfactory epithelium either at the end of the exposure or during the observation period of 6 months (Table 1).

In the 1996 supplement (supplement "n-Butyl acrylate" 1999), the lower 95% confidence limits of the benchmark concentrations for a 5% increase in the incidence

Table 2 Estimated benchmark concentrations for *n*-butyl acrylate (supplement "n-Butyl acrylate" 1999)

End point	Time (months)	Benchmark concentration (ml/m³)	
		males	females
reserve cell hyperplasia[1)]	24	2.7	2.8
	24 + 6	11.5	25.4
	total	11.6	9.6
reserve cell hyperplasia[2)]	24	2.9	2.6
	24 + 6	not determinable	16.8
	total	6.1	7.7
atrophy	24 + 6	6.9	not determinable

[1)] with the loss of olfactory or ciliated cells
[2)] with and without the loss of olfactory or ciliated cells

($BMDL_{05}$) were calculated for these end points (Table 2). However, no information was provided about the software and models used.

Reserve cell hyperplasia with the loss of olfactory or ciliated cells was identified as the most sensitive end point after exposure for 24 months with a $BMDL_{05}$ of 2.7 to 2.8 ml/m³ (supplement "n-Butyl acrylate" 1999). A MAK value of 2 ml/m³ was established in view of the higher sensitivity of the rat resulting from the higher exposure of the olfactory epithelium compared with that in humans, and the reversibility of the findings in some cases.

With the BMDS software 2.3.1 of the US EPA very similar $BMDL_{05}$ values of 3.0 and 2.8 ml/m³, respectively, were obtained for this end point for male rats (restricted multistage 2-degree model) and female rats (identical values were obtained with the restricted gamma, restricted Weibull and Quantal linear models) (Figure 1 and Figure 2). This confirmed the previous benchmark calculation with a $BMDL_{05}$ of about 3 ml/m³.

The NOAEC for systemic toxicity was the highest tested concentration of 135 ml/m³ (documentation "n-Butyl acrylate" 1993).

Allergenic effects

Sensitizing effects on the skin

A local lymph node assay in CBA/Ca mice yielded an EC3 value of 11.2% for *n*-butyl acrylate tested in acetone/olive oil (4:1) (Dearman et al. 2007). *n*-Butyl acrylate was therefore found to have a moderate to weak sensitizing potential in this test system.

In an earlier study, *n*-butyl acrylate concentrations of 20% and 30%, but not the 10% concentration, induced increased lymphocyte proliferation in B6C3F1 mice compared with the incidence in control animals (Hayes and Meade 1999).

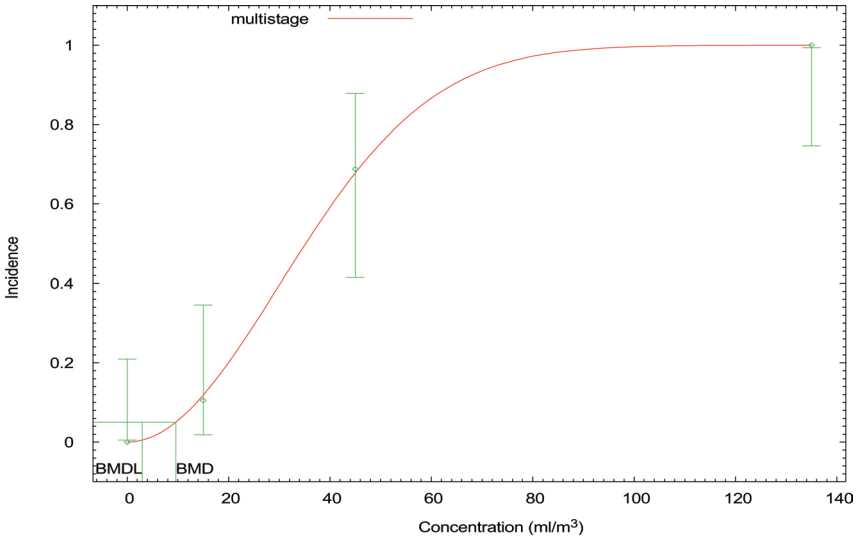

Figure 1 Calculated benchmark dose for male rats for the end point "reserve cell hyperplasia with the loss of olfactory or ciliated cells" after 24 months, multistage model 2-degree polynomial with parameter restriction; BMD_{05} = 9.6 ml/m³, $BMDL_{05}$ = 3 ml/m³

However, when the same concentrations were used for induction, a negative result was obtained in a mouse ear swelling test after challenge with a 30% formulation (Hayes and Meade 1999).

Sensitizing effects on the airways

There are no data available.

Developmental toxicity

In two developmental toxicity studies with Sprague Dawley rats, NOAECs of 25 and 100 ml/m³ and LOAECs (lowest observed adverse effect concentrations) of 135 and 200 ml/m³ were obtained. The NOAEC was thus 100 ml/m³. In an oral developmental toxicity study in mice, the NOAEL (no observed adverse effect level) was 1000 mg/kg body weight and day (supplement "n-Butylacrylat" 2007, available in German only).

Genotoxicity

The data from the 1996 supplement are described below (supplement "n-Butyl acrylate" 1999).

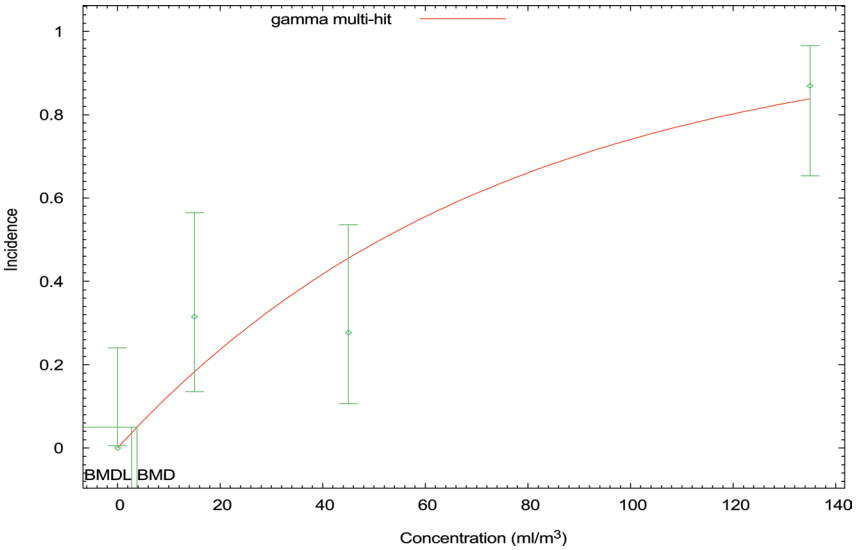

Figure 2 Calculated benchmark dose for female rats for the end point "reserve cell hyperplasia with the loss of olfactory or ciliated cells" after 24 months, gamma model with parameter restriction; BMD_{05} = 3.8 ml/m³, $BMDL_{05}$ = 2.8 ml/m³

In vitro

n-Butyl acrylate was not found to have mutagenic effects in Salmonella typhimurium. An UDS test in SHE cells (a cell line derived from Syrian hamster embryo) yielded negative results. A small increase in the incidence of sister chromatid exchange was observed in CHO cells (a cell line derived from Chinese hamster ovary). However, as the incidence was less than twice that obtained in the control group, this finding is not relevant. *n*-Butyl acrylate did not cause clastogenic effects in two micronucleus tests in vitro. In CHO cells, chromosomal aberrations were induced only at severely cytotoxic concentrations without the addition of a metabolic activation system. Therefore, the result is of no relevance. A small increase in the incidence of chromosomal aberrations was observed after the addition of a metabolic activation system. As the incidence was less than twice that observed in the control group, the relevance of these results is questionable.

In vivo

In Drosophila melanogaster, 1800 ppm *n*-butyl acrylate administered with the diet or by injection did not induce an increase in sex-linked recessive lethal mutations.

There was no evidence of a chromosome-damaging effect on the bone marrow of Chinese hamsters or Sprague Dawley rats exposed to *n*-butyl acrylate concentrations of 820 ml/m³ by inhalation (3 days for 6 hours and 1 day for 5 hours; concentration in the lethal range). An increased incidence of chromosomal aberrations

was observed both after single oral *n*-butyl acrylate doses of 300 and 600 mg/kg body weight (1/4 and 1/2 LD_{50}) and after 8-week oral administration of 300 mg/kg body weight (2×/week; dissolved in vegetable oil). This study provides evidence of a possible clastogenic effect of *n*-butyl acrylate in rats after oral administration; in view of the negative findings obtained in the inhalation study this needs further clarification.

There are no new data available for genotoxicity.

Carcinogenicity

In the above-described 2-year study in rats with exposure up to 135 ml/m³, *n*-butyl acrylate was not carcinogenic and was therefore not classified in any of the categories for carcinogenicity (documentation "n-Butyl acrylate" 1993).

Manifesto (MAK value/classification)

The critical effects in a 2-year study were reserve cell hyperplasia with the loss of cilia and olfactory cells in the olfactory epithelium of rats.

MAK value. Recalculation of the benchmark concentrations of the 2-year study using the US EPA BMDS programme confirmed a $BMDL_{05}$ in the range of 3 ml/m³. A NAEC (no adverse effect concentration) of 5 ml/m³ is obtained from the LOAEC of 15 ml/m³ by dividing the LOAEC by a factor of 3 according to the method of Brüning et al. (2014). MAK values of 1 and 2 ml/m³ were calculated from the $BMDL_{05}$ and the NAEC to extrapolate the effects in the olfactory epithelium of rats to a NOAEC for humans (1:2), taking into consideration the preferred value approach. In order to decide which of the two values is to be preferred, volunteer studies of sensory irritation would need to be included in the evaluation. Although no such studies are available for *n*-butyl acrylate, a number of studies have been carried out for ethyl acrylate, which is closely related in terms of structure. As local irritation is likewise the critical effect of ethyl acrylate, the results can be used to evaluate the local irritation of *n*-butyl acrylate. The RD_{50} of ethyl acrylate is similar to that of *n*-butyl acrylate (Section "Acute Toxicity") and ethyl acrylate was found to have a very similar NOAEC in a medium-term study in rats (*n*-butyl acrylate: 21 ml/m³; ethyl acrylate: 25 ml/m³) and a NOAEC of 5 ml/m³ in a 2-year study in rats. As there was no evidence of sensory irritation in a 4-hour volunteer study with ethyl acrylate concentrations of 2.5 ml/m³ and peaks of up to 5 ml/m³ (supplement "Ethylacrylat" 2016, available in German only), a MAK value of 2 ml/m³ was established. On the basis of its similarity with the more thoroughly investigated ethyl acrylate, the previously established MAK value of 2 ml/m³ has been confirmed for *n*-butyl acrylate.

Peak limitation. In analogy to ethyl acrylate and on the basis of the volunteer study, the previous classification in Peak Limitation Category I with an excursion factor of 2 has been confirmed for *n*-butyl acrylate.

Prenatal toxicity. The 50-fold margin between the NOAEC of 100 ml/m³ for developmental toxicity in rats and the MAK value of 2 ml/m³ is sufficiently high. A NOAEL of 1000 mg/kg body weight and day was determined in an oral study in mice. This is converted according to the new toxicokinetic procedure. The following toxicokinetic data are used to extrapolate this NOAEL in rats to a concentration in workplace air: the corresponding species-specific correction value for the mouse determined on the basis of the toxicokinetic data (1:7), the oral absorption of 100% (experimental determination for rats; ECHA 2015 a), the body weight (70 kg) and the respiratory volume (10 m³) of the person, and the assumed 100% absorption by inhalation. A concentration of 1000 mg/m³ was calculated from this (188 ml/m³). Therefore, the 94-fold margin between the concentration calculated from the data in mice and the MAK value is sufficient and classification in Pregnancy Risk Group C has been confirmed.

Germ cell mutagenicity and carcinogenicity. *n*-Butyl acrylate was marginally clastogenic in vitro. Evidence of a clastogenic effect after oral administration in rats was not substantiated in an inhalation study. *n*-Butyl acrylate was not carcinogenic in an inhalation study in rats. Therefore, *n*-butyl acrylate has not been classified in any of the germ cell mutagen or carcinogen categories.

Absorption through the skin. Dermal absorption of up to 1070 mg after exposure to a saturated aqueous solution or of up to 8000 mg after exposure to a non-irritative solution has been estimated for humans from a model calculation assuming the exposure of a 2000 cm² skin surface area for 1 hour. The NOAEC for chronic systemic effects in rats was 135 ml/m³ (718 mg/m³) after 2 years. Based on this value, a concentration of 180 mg/m³ is obtained taking into consideration the increased respiratory volume at the workplace (1:2) and extrapolation from an animal study (1:2). At a respiratory volume of 10 m³ in 8 hours and 100% absorption, this corresponds to a tolerable dose of 1800 mg *n*-butyl acrylate for systemic effects in humans. The results of the model calculations indicate that the amount absorbed through the skin is higher than 25% of the systemically tolerable amount. *n*-Butyl acrylate is therefore designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. Only a few reports of contact sensitization induced by *n*-butyl acrylate have become available since the 1999 supplement (supplement "n-Butyl acrylate" 2001). However, positive results in two local lymph node assays have confirmed the substance has contact allergenic potential. There are no data available for sensitizing effects on the respiratory tract. Therefore, *n*-butyl acrylate is designated with "Sh" (for substances which cause sensitization of the skin), but not with "Sa" (for substances which cause sensitization of the airways).

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