Table 4
Absolute and relative organ weights in male and female rats exposed to furfural by inhalation for 28 days

	Kidneys		Liver		Spleen	
	Absolute (g)	Relative (g/kg)	Absolute (g)	Relative (g/kg)	Absolute (g)	Relative (g/kg)
Males						
Control	1.37 ± 0.02	6.79 ± 0.06	5.60 ± 0.13	27.7 ± 0.3	0.456 ± 0.014	2.26 ± 0.05
20 mg/m^3	1.46 ± 0.04	6.58 ± 0.05	6.01 ± 0.11	27.0 ± 0.2	0.509 ± 0.011	2.29 ± 0.02
40 mg/m^3	1.39 ± 0.05	6.59 ± 0.05	6.18 ± 0.22	29.4 ± 1.0	0.500 ± 0.017	2.37 ± 0.06
80 mg/m^3	1.44 ± 0.05	7.11 ± 0.19	7.29 ± 0.74**	35.8 ± 3.3**	0.502 ± 0.012	2.47 ± 0.03**
160 mg/m^3	1.40 ± 0.01	6.80 ± 0.05	5.68 ± 0.14	27.5 ± 0.4	0.474 ± 0.008	2.30 ± 0.02
320 mg/m^3	1.39 ± 0.01	6.97 ± 0.13	5.99 ± 0.28	30.1 ± 1.8	0.475 ± 0.006	2.38 ± 0.05
160 mg/m$^{3\#}$	1.36 ± 0.06	6.48 ± 0.09	5.39 ± 0.22	25.8 ± 0.3	0.497 ± 0.023	2.38 ± 0.07
320 mg/m$^{3\#}$	1.39 ± 0.04	6.70 ± 0.06	5.56 ± 0.19	26.8 ± 0.3	0.471 ± 0.012	2.28 ± 0.03
640 mg/m$^{3\#}$	1.37 ± 0.03	6.75 ± 0.05	5.82 ± 0.36	28.7 ± 1.5	0.453 ± 0.008	2.24 ± 0.02
Females						
Control	0.95 ± 0.04	7.19 ± 0.20	4.23 ± 0.42	31.9 ± 2.8	0.352 ± 0.010	2.66 ± 0.06
20 mg/m^3	1.01 ± 0.03	7.70 ± 0.11	3.67 ± 0.07	28.0 ± 0.4	0.333 ± 0.021	2.53 ± 0.10
40 mg/m^3	0.97 ± 0.03	7.44 ± 0.12	3.78 ± 0.11	28.9 ± 0.7	0.337 ± 0.011	2.57 ± 0.05
80 mg/m^3	0.98 ± 0.03	7.43 ± 0.11	3.79 ± 0.04	28.7 ± 0.6	0.356 ± 0.007	2.70 ± 0.03
160 mg/m^3	1.02 ± 0.02	7.64 ± 0.11	3.90 ± 0.12	29.3 ± 0.8	0.324 ± 0.006	2.43 ± 0.06
320 mg/m^3	1.00 ± 0.02	7.72 ± 0.24	3.75 ± 0.05	28.9 ± 0.6	0.343 ± 0.012	2.64 ± 0.05
160 mg/m$^{3\#}$	0.95 ± 0.03	7.54 ± 0.13	3.34 ± 0.07**	26.4 ± 0.5**	0.326 ± 0.007	2.58 ± 0.06
320 mg/m$^{3\#}$	1.00 ± 0.01	7.45 ± 0.12	3.69 ± 0.08	27.4 ± 0.6*	0.317 ± 0.003	2.35 ± 0.05**
640 mg/m$^{3\#}$	0.99 ± 0.02	7.53 ± 0.15	3.56 ± 0.05**	27.0 ± 0.5*	0.336 ± 0.014	2.54 ± 0.06

Groups of 5 male and 5 female rats were exposed by inhalation to furfural 6 h/day, 5 days/week for 28 days. Animals were necropsied the day after the last treatment, and organs were weighed.

#Exposure lasted 3 h/day. Statistics: ANOVA-Dunnett's test; *$p < 0.05$, **$p < 0.01$.

of 6 male rats (also replaced due to early mortality). Although the cause(s) of death could not be established, the fatalities were considered to be treatment-related. The dose levels used were based on a 16-day gavage study in rats of the same strain in which mortality was observed at 240 mg/kg (Irwin, 1990). These values were, however, higher than reported LD50 values for rats, i.e. between 50 and 127 mg/kg bw (Castelli et al., 1967; RTECS, 2002). Because these latter studies were rather old (reported in the 60s) and no information was available on purity these studies were considered less valuable to establish dose levels. The other changes that might be of toxicological relevance in our study were the increases in absolute and relative kidney weight in both surviving females of the high dose group and increases in absolute and relative liver weight in one out of these 2 rats. These increases in organ weight were, however, not accompanied by histopathological changes. Moreover, the small size of the group may hamper proper interpretation of the results. In the NTP studies mentioned above (Irwin, 1990), however, increases in mean absolute and relative liver and kidneys weights were also observed, i.e. in male rats exposed to 90 mg/kg bw/day for 90 days. Also, treatment-related histopathological changes were absent (Irwin, 1990). In long-term oral studies with furfural in rats and mice, the liver appeared to be the target organ and indeed exhibited the greatest susceptibility to the test compound (Shimizu, 1986; Shimizu et al., 1989; Irwin, 1990). Because the increase in spleen weight in females treated with the next lower dose level of 96 mg/kg bw/day was not dose-related and was not accompanied by histopathological changes, the change in spleen weight was not considered to be toxicologically relevant. Based on the mortality observed following oral administration of furfural to rats for up to 28 days at dose levels of 120–192 mg/kg bw/day, and the absence of treatment-related effects at the next lower level tested, i.e. 96 mg/kg bw/day, the no-observed-adverse-effect level (NOAEL) was placed at the latter level, indicating a very steep dose-response curve.

Since long-term inhalation toxicity studies with furfural in rats and hamsters had shown exposure-related local changes only, i.e. histopathological changes in the nasal cavity (Feron et al., 1979), or lungs (Gupta et al., 1991; Mishra et al., 1991) at relatively high concentrations of approximately 149–448 mg/m^3, the goal of the present study was to investigate whether route-to-route extrapolation could be used to derive limit values for inhalation exposure from oral toxicity data. The present inhalation toxicity study with furfural indicated that exposure of rats for 5 days/week for 28 days resulted in mortality at concentrations of 640 mg/m^3 (6 h/day) (3840 mg/m^3 h) and above within 1–8 days. Although a 4-h LC50 value of 600 mg/m^3 in rats had been reported in 1972 (RTECS, 2002), more value was placed at the reported 1-h LC50 value of 4075 mg/m^3 (Terrill et al., 1989) to establish the concentration levels to be used.

At 640 mg/m^3 (3 h/day; 1920 mg/m^3 h) and at 320 mg/m^3 (6 h/day; 1920 mg/m^3 h) and below, however, exposure was tolerated without serious clinical effects. If it is

Table 5
Nasal histopathological changes in male animals (Panel A) and female animals (Panel B) exposed to furfural by inhalation

	0 mg/m^3	20 mg/m^3	40 mg/m^3	80 mg/m^3	160 mg/m^3	320 mg/m^3	160 mg/m$^{3\#}$	320 mg/m$^{3\#}$	640 mg/m$^{3\#}$
Panel A[a]									
TRESM									
Very slight	1	1	0				1		2
Slight		3	4				1	2	2
Moderate		1	1	5	2	3	2	1	
Severe					3	2			
Total	1	5*	5*	5*	5*	5*	4	3	4
TREAH									
Very slight	1								1
Slight		4					3	3	4
Moderate		1	4	1	1	2	2	2	
Severe			1	4	4	3			
Total	1	5*	5*	5*	5*	5*	5*	5*	5*
RESM									
Very slight				1	4	1			
Slight					1	1		1	
Total	0	0	0	1	5**	2	0	1	0
REAH									
Very slight				1			1	1	2
Slight			1	1	3	1	1	1	1
Moderate				1	2	1		1	
Severe						2			
Total	0	0	1	3	5**	4*	2	3	3
OED									
Very slight				1	3	1	1	3	2
Slight					1	2		2	1
Moderate						2			
Total	0	0	0	1	4*	5**	1	5**	3
Panel B[b]									
TRESM									
Very slight									1
Slight		5	1	1	1		4	3	2
Moderate			3	2	1	4	1	2	2
Severe			1	2	3	1			
Total	0	5**	5**	5**	5**	5**	5**	5**	5**
TREAH									
Slight		2	1			1	1	3	1
Moderate		3	1	1	3	2	4	1	4
Severe			3	4	2	2		1	
Total	0	5**	5**	5**	5**	5**	5**	5**	5**

Table 5 (*continued*)

	0 mg/m³	20 mg/m³	40 mg/m³	80 mg/m³	160 mg/m³	320 mg/m³	160 mg/m³#	320 mg/m³#	640 mg/m³#
RESM									
Very slight					2	2		1	2
Slight					1		1		
Total	0	0	0	0	3	2	1	1	2
REAH									
Very slight		1		1		1			
Slight		1	1	1	2	4	2	4	3
Moderate					3				1
Total	0	2	1	2	5**	5**	2	4*	4*
OED									
Very slight				3		1	1	2	2
Slight				1	1	2	2	1	3
Moderate					2	2		1	
Total	0	0	0	4*	3	5**	3	4*	5**

Groups of 5 male and 5 female rats were exposed by inhalation to furfural 6 h/day, 5 days/week for 28 days. Animals were necropsied the day after the last treatment, and the nose was preserved for histopathgological examination. #Exposure lasted 3 h/day. TRESM = transitional respiratory epithelial squamous metaplasia; TREAH = transitional respiratory epithelial atypical hyperplasia; RESM = respiratory epithelial squamous metaplasia; REAH = respiratory epithelial atypical hyperplasia; OED = olfactory epithelial disarrangement. Statistics: two-sided Fisher's exact test; $^{*}p < 0.05$, $^{**}p < 0.01$.

When expressed as a Probit relation, viz. $P = C^n \cdot T$ or, $P = b_0 + b_1 \ln C + b_2 \ln T$ with $n = b1/b2$ (Finney, 1977) examining the relationship between exposure concentration and duration, the following Probit relations were obtained with C (concentration) in mg/m³ and T (time) in hours, using very slight as gradation 1, slight as gradation 2, etc., indicating a maximum response of 20 (5 animals times the maximum gradation of severe (=4)):

[a]TRESM: $P = -0.86 + 0.21 \ln C + 2.14 \ln T$ ($n = 0.10$).

TREAH: $P = 1.92 + 0.12 \ln C + 1.99 \ln T$ ($n = 0.06$).

REAH: $P = -2.12 + 0.64 \ln C + 2.11 \ln T$ ($n = 0.30$).

OED: $P = -2.50 + 0.79 \ln C + 1.54 \ln T$ ($n = 0.51$).

For RESM no proper Probit relation could be obtained.

[b]TRESM: $P = 2.66 + 0.10 \ln C + 1.43 \ln T$ ($n = 0.07$).

TREAH: $P = 4.15 - 0.06 \ln C + 1.13 \ln T$ (n = not applicable).

REAH: $P = 0.93 + 0.39 \ln C + 0.99 \ln T$ ($n = 0.40$).

OED: $P = -0.34 + 0.58 \ln C + 1.08 \ln T$ ($n = 0.54$).

For RESM no proper Probit relation could be obtained.

assumed that all inhaled furfural is absorbed and that the ventilation of the rat in one minute is 0.8 l/kg bw, then the non-lethal concentrations of 640 mg/m^3 (3 h/day) and 320 mg/m^3 (6 h/day) are equivalent to a daily oral dose (also assuming total absorption) of 92 mg/kg bw/day. This dose is comparable to the value of 96 mg/kg bw/day which was the highest oral level tolerated without mortality, although it should be noted that the oral doses were given 7 days per week whereas inhalation exposure took place during 5 days per week. Also, absorption data are only known for the inhalation route. For humans, an absorption value of 78% of the inhaled amount was reported (Flek and Sedivic, 1978). For the oral route no values were found. However, based on the high concentrations observed in liver and kidneys and the rapid liver metabolism (Nomeir et al., 1992), absorption of furfural following oral intake should be considerable. In contrast to systemic effects, local effects, i.e. histopathological nasal changes were seen even at the lowest concentration of 20 mg/m^3 (120 mg/m^3 h). With increasing exposure concentration, the effects increased in incidence and severity and also expanded from the respiratory epithelium in the anterior part to the posterior part, including the olfactory epithelium. Aldehydes, such as furfural, constitute a group of relatively reactive organic compounds, known to interact with cellular macromolecules such as thiols, protein and/or DNA (Feron et al., 1991; Cassee and Feron, 1994; Grafstrom et al., 1994; Conaway et al., 1996). Upon inhalation exposure to the aldehydes formaldehyde, acetaldehyde and acrolein, histopathological and biochemical changes in the respiratory and olfactory epithelium of the nose were observed (Cassee et al., 1996) in a comparable way as observed for furfural with regard to histopathological changes (present study) or with regard to biochemical changes in the lungs (Gupta et al., 1991).

From the results of the present 28-day inhalation study it was concluded that the no-adverse-effect-level (NAEL) for local toxicity of furfural is lower than 20 mg/m^3, whereas the NOAEL for systemic inhalation toxicity was at least 16 times higher, viz. 320 mg/m^3 (6 h/day) or 640 mg/m^3 (3 h/day). In hamsters, exposure to a concentration of 448 mg/m^3 furfural for 6 h/day, 5 days/week for 13 weeks induced atrophy and hyperplasia of the nasal olfactory epithelium. No changes were observed at a level of 77 mg/m^3 (Feron et al., 1979). Damage of the nasal mucosa (atrophy and downward growth of sensory cells of the olfactory epithelium, degenerative changes in Bowman's glands, and occurrence of cyst-like structures in the lamina propria beneath the olfactory epithelium) was also found in hamsters exposed to furfural during 12 months to initially 1550 mg/m^3, followed by 970 mg/m^3 during the last 32 weeks (Feron and Kruysse, 1978). These data indicate a much higher susceptibility of rats in comparison to hamsters, which was also shown in acute inhalation toxicity studies (Kruysse, 1972; Terrill et al., 1989; Gupta et al., 1991; RTECS, 2002). A higher susceptibility of rats compared to hamsters was also found for inhalation of other aldehydes as formaldehyde, acetaldehyde, and acrolein (Kruysse et al., 1975; Feron et al., 1978; Appelman et al., 1982; Feron et al., 1989). Moreover, with respect to oral toxicity, rats were also more susceptible than mice (Castelli et al., 1967; Irwin, 1990; RTECS, 2002). These data may suggest species (rat) specificity of these findings which may be relevant in human risk assessment. Although the lowest level tested in our study (viz. 20 mg/m^3) still resulted in nasal changes, this level may have been close to concentrations at which workers had been exposed as it was reported that exposure of workers exceeding a concentration of 8 mg/m^3 resulted in respiratory tract irritation (Apol and Lucas, 1975; Di Pede et al., 1991).

To examine if exposure-related changes observed were more related to concentration or to duration, 3-h exposure groups were included in the study design in addition to the conventional 6-h exposure groups. Although in the present inhalation study mortality occurred at 640 mg/m^3 (6 h/day; 3840 mg/m^3 h) and at 1280 mg/m^3 (3 h/day; also 3840 mg/m^3 h), effects at lower concentrations were practically absent. This indicated not only that for the endpoint mortality the concentration-response relation must be steep but also that mortality in the range tested is related to the total dose (concentration $\times$ duration = mg/m^3 h), and less to the concentration alone or the number of hours the animals were exposed. Because of the absence of systemic effects at lower concentrations, the similarity of the effects of daily exposure for 6 h and effects of daily exposure at a doubled concentration for 3 h could not be investigated. Local effects, i.e. the histopathological changes in the nasal passages of animals exposed for 3 h/day were, with respect to incidence and degree, much less than the changes seen in animals exposed to the same daily 'dose', i.e. at half the concentration for 6 h/day. This indicates that the changes observed, in contrast to mortality, were more related to exposure duration than exposure concentration or total exposure (mg/m^3 h). This was evidenced by establishing Probit relations examining the relationship between exposure duration and concentration (Finney, 1977; see also the note underneath Table 5). If Haber's rule (Haber, 1924; Witschi, 1999) would have been valid, n values would have been 1, or the contribution of exposure concentration would have been similar to that of exposure duration. Especially for histopathological effects at the level of the transitional respiratory epithelium (TRESM and TREAH), however, the contribution of the exposure duration was at least tenfold the contribution of the exposure concentration (n values between 0.06 and 0.10; Table 5). With regard to effects on the respiratory

(REAH) and olfactory epithelium (OED), the contribution of the exposure duration was two- to threefold the contribution of the exposure concentration (n values between 0.30 and 0.54; Table 5).

Overall, mortality occurred at comparable external dose levels by the oral and inhalation route, i.e. 192 mg/kg bw/day orally and 184 mg/kg bw/day inhalatory (corresponding to 640 mg/m^3 (6 h/day; 3840 mg/m^3 h) or 1280 mg/m^3 (3 h/day; 3840 mg/m^3 h)), assuming 100% absorption. The oral study did not show any evidence of irritation or local toxicity (e.g. at the forestomach) at lower levels. Furfural might be less irritating dissolved in corn oil than as a vapour. For instance, acrolein vapour is extremely irritating to the nasal and tracheal mucosa of rodents but administration in the drinking water to rats has not been reported to cause gastric damage (Feron et al., 1991). Based on the absence of local effects at the portal of entry, it would have been permitted to perform route-to-route extrapolation from the oral to the inhalation route. However, even when applying a safety/uncertainty factor of 2–3, the present inhalation study shows that a large discrepancy exists. The histopathological nasal changes observed at much lower concentrations, even at the lowest tested concentration of 20 mg/m^3, prove that for locally acting substances such as furfural extrapolation from the oral to the inhalation route is not valid. Comparing the orally obtained NOAEL of 96 mg/kg bw/day with the lowest tested inhalation concentration of 20 mg/m^3 (corresponding to 6 mg/kg bw/day) which still induced local effects, furfural appears to be at least 16 times more toxic by inhalation than by oral gavage (based on external doses).

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