June 2023

The SCOEL recommendation document covers the following substances:

Substance name	EC number	CAS RN
o-Cresol	202-423-8	95-48-7
m-Cresol	203-577-9	108-39-4
p-Cresol	203-398-6	106-44-5
Cresol (all isomers)	215-293-2	1319-77-3

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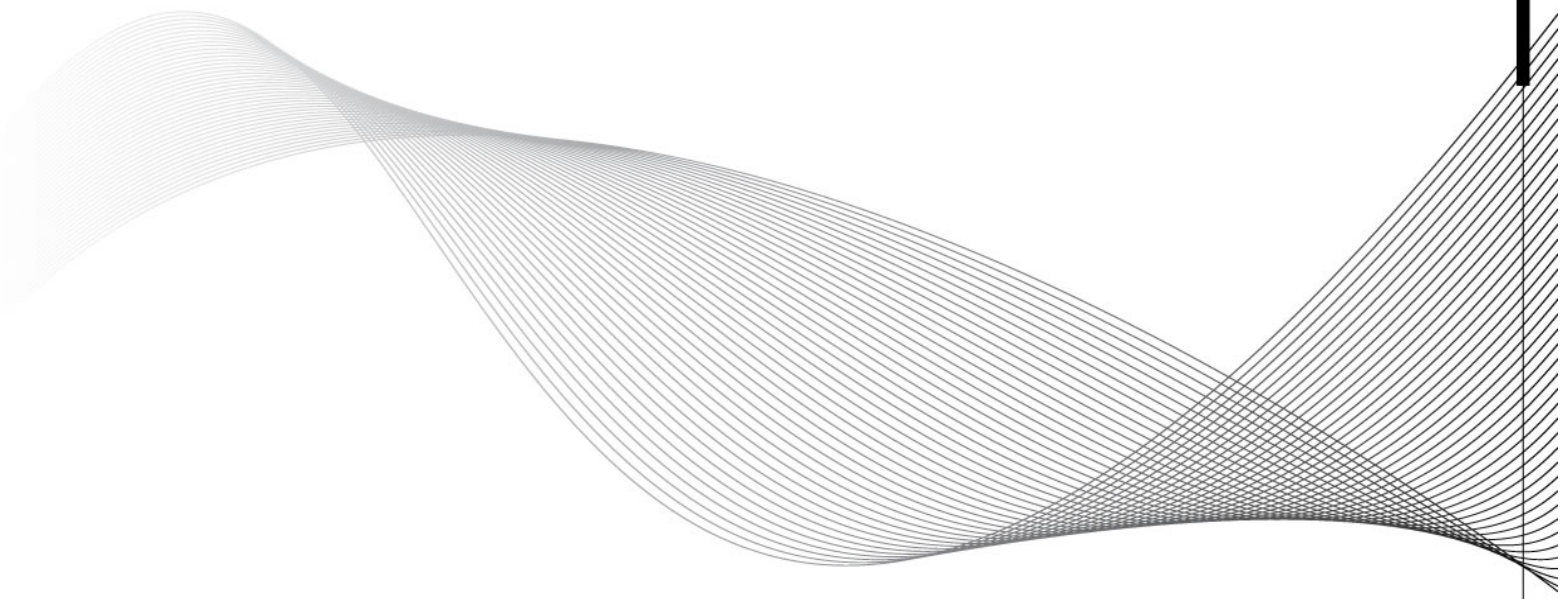
Social Europe



Recommendation from the Scientific Committee on Occupational Exposure Limits for cresol (all isomers)

SCOEL/SUM/96

March 2002

European Commission

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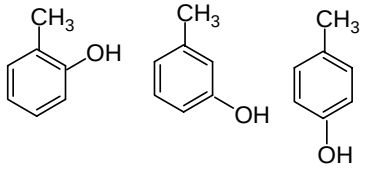
8 hour TWA:	no recommendation made
STEL (15 min):	-
Additional classification:	"skin"

Substance

Cresol (all isomers)



Synonyms :

Isomer	Chemical name (CAS)	Synonyms	CAS N°
o-cresol	2-methylphenol	*o*-cresylic acid 1-hydroxy-2-methylbenzene 2-hydroxy toluene	95-48-7
m-cresol	3-methylphenol	*m*-cresylic acid 1-hydroxy-3-methylbenzene 3-hydroxy toluene	108-39-4
p-cresol	4-methylphenol	*p*-cresylic acid 1-hydroxy-4-methylbenzene 4-hydroxy toluene	106-44-5

EINECS N° (all isomers)	:	215-293-2
EEC N° (all isomers)	:	604-004--00-9
Classification	:	
CAS N° (all isomers)	:	1319-77-3
MWt (all isomers)	:	108.14
Conversion factor	:	1 mg/m^3 = 0.227 ppm

This summary is based on criteria documents on cresol (all isomers) from the Dutch Expert Committee on Occupational Standards of the Health Council of the Netherlands (DECOS 1998), the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area of the Deutsche Forschungsgemeinschaft (Greim 2000), the International Programme on Chemical Safety of the World Health Organization (WHO 1995), and from the TLV Committee of the American Conference of Governmental Industrial Hygienists (ACGIH 1991).

1. Occurrence/use

Commercial cresol is a mixture of the ortho-, meta-, and para-isomers of cresol, in which the *m*-isomer predominates, and contains not more than 5% phenol. The mixture is derived from coal tar or petroleum (ACGIH 1991). *o*-Cresol and *p*-cresol occur as crystalline solids or yellowish liquids, *m*-cresol as a colourless to yellow liquid. Tricresol, a commercially available mixture of the three isomers, is a colourless to yellow or violet liquid. All cresol isomers have a strong phenolic odour (Greim 2000).

	Melting point (°C)	Boiling point (°C)	Density at 20°C (g/cm^3)	Vapour pressure at 25°C (hPa)	Log P_{ow}
o-cresol	30.9	191.0	1.03	0.39	1.95
m-cresol	11.5	202.2	1.03	0.19	1.96
p-cresol	34.8	201.9	1.02	0.15	1.94

Cresol, as a mixture, is used as an ore flotation agent; as a disinfectant; and in the manufacture of synthetic resins, chemicals, dyes, and antioxidants. *m*-Cresol is used as a fumigant and in photographic developers and explosives. Inhalation of appreciable amounts of cresol vapour is unlikely under normal conditions because of its low vapour pressure. Hazardous concentrations may develop at elevated temperatures (ACGIH 1991).

2. Health significance

Cresol isomers are strong eye and skin irritating compounds. No adequate inhalation studies are available. The results of repeated-dose oral toxicity studies do not clearly indicate significant differences with respect to the toxicity of the various isomers. In 28-day feeding studies on rats and mice, effects on liver and kidney weights were observed, though not accompanied with histopathological changes. In 13-week studies with rats, decreased body weight gain, mild anaemia or increased total protein were observed in low dose groups (150-175 mg/kg bw/day). In higher dose groups ($\geq$450 mg/kg bw/day), central nervous system-related effects and mortality were seen.

2.1. Metabolism and toxicokinetics

Cresol isomers are readily taken up from the gastrointestinal tract and also through the skin (DECOS 1998).

The isomers are mainly conjugated with glucuronic acid and sulfate, and to a lesser extent are oxidized to dihydroxy metabolites or hydroxybenzoic acid (*p*-cresol). *p*-Cresol is also metabolized to a reactive quinone-methide intermediate (DECOS 1998; Greim 2000).

The primary excretion route is urinary excretion, *o*-conjugates being the most important constituents accounting for 60-70% of the administered dose (DECOS 1998).

After application of a *p*-cresol dose of 4 µg/cm^2 to the isolated skin of hairless mice, the total amounts of substance absorbed after 6, 12 and 24 hours were 69 $\pm$ 6%, 74 $\pm$ 4% and 77 $\pm$ 3% of the dose. After two hours the maximum rate of penetration was measured, and found to be 25 $\pm$ 3.9% of the dose per hour (Hinz et al. 1991). The high penetration rate was perhaps a result of cresol-induced skin damage because the *p*-cresol was applied in a

rapidly volatile solvent (50 µg acetone). However, for a cresol concentration of 1%, which is no longer irritating to the skin, applied for 1 hour to a skin area of 2000 cm^2, the model of Fiserova-Bergerova et al. (1990) predicts dermal uptake of 3230 mg and that of Guy and Potts (1993) 190 mg. When these data are compared with the systemic NOEL of about 50 mg/kg body weight derived from animal studies (calculated uptake through 2000 cm^2 skin is about 3500 mg) it is clear that uptake through the skin is relevant for exposure.

2.2. Acute toxicity

In an unpublished US study, it was reported that exposure to (theoretically) maximum concentrations (calculated to be 1220 and 710 mg/m^3 for *o*- and *m*-/*p*-cresol, respectively) for one hour was not lethal to rats during the observation period of 14 days after the exposure. In other reports, mean lethal concentrations of 29-58 and 178 mg/m^3 were presented for rats and mice respectively (exposure periods and other relevant data not available). In mice, signs of toxicity included muscle twitching progressing to clonic convulsions, haematuria, and necrotic degenerative changes in the lung and liver as well as respiratory tract irritation (DECOS 1998).

Oral LD_{50} values for rats are 121, 242 and 207 mg/kg bw for *o*-, *m*-, and *p*-cresol, respectively. Dermal LD_{50} values were determined in rabbits with 890 and 1380 mg/kg bw (*o*-cresol), 2830 and 2050 mg/kg bw (*m*-cresol) and 300 mg/kg bw (*p*-cresol) (DECOS 1998).

2.3. Local effects

Respiration tract: Respiratory tract irritation has been found in mice, rats, and cats following single or short-term exposure to concentrations of an o-cresol vapour/aerosol mixture in concentrations ranging from 5-10 to 178 mg/m^3 (DECOS 1998).

In repeated dose feeding studies, mainly *p*-cresol and a mixture of *m*- and *p*-cresol induced histopathological changes in the nasal cavity. These lesions may have been the result of either direct contact of the nose with the compounds in feed or of exposure to their vapours (DECOS 1998).

Skin and eyes: On the skin and eyes, the cresol isomers are highly irritating or even caustic. Intensive skin contact or a single oral dose can have systemic effects and cause even coma and death. After application of individual cresol isomers or a mixture of isomers to the skin of rabbits for 4 hours, severe skin irritation was observed. Treatment of an area of dorsal skin of the mouse 3 times weekly for 6 weeks with a 0.5% solution of *p*-cresol in acetone caused depigmentation of skin and hair. This effect was not seen with the other isomers. The instillation of undiluted cresol isomers into the rabbit eye according to the Draize method resulted in extreme irritation (DECOS 1998).

2.4. Sensitisation

Using a modified Draize procedure, *p*-cresol did not induce sensitisation in guinea pigs (injection challenge concentration: 0.1%; application challenge concentration: 10%) (DECOS 1998: Sha78). In another study in which a 7.5% solution of a mixture of *m*-cresol and *p*-cresol in acetone was repeatedly applied to the skin of guinea pigs, sensitisation was not observed (DECOS 1998).

2.5. Toxicity after repeated exposure

Inhalation:

Uzhdavini et al. (1972) exposed mice to a mixture of *o*-cresol aerosol and vapour 2 h/day, 6 days/week for 1 month; exposure concentrations varied from 26 to 76 mg/m^3, with an average of 50 mg/m^3. No mortality was recorded. Clinical signs of toxicity during the daily exposure periods were limited to signs of respiratory irritation at the start of the exposure, followed by a period of hypoactivity lasting until the end of the exposure. The tails of some animals mummified and fell off after 18-20 days. Body weight gain was slightly reduced compared to controls. Microscopic examination revealed signs of irritation in the respiratory tract; these included oedema, cellular proliferation, and small haemorrhages in the lung. Other lesions included degeneration of heart muscle, liver, kidney and nerve cells and glial elements of the central nervous system (WHO 1995).

Rats were exposed to an average concentration of 9 ± 0.9 mg/m^3 of *o*-cresol vapour 5 days/week for 4 months. The first 2 months, exposure was 6 h/day, the last two months 4 h/day (Uzhdavini et al. 1972). The number of animals and strain was not reported in the study. Effects of *o*-cresol exposure in rats included accelerated loss of conditioned defensive reflex, leukocytosis, decreased erythroid/myeloid ratio in the bone marrow, increased duration of hexanol narcosis (indicating possible impaired liver function) and morphological changes in respiratory tissues (inflammation and irritation of the upper respiratory tract, oedema, and perivascular sclerosis in the lungs) (WHO 1995).

Oral application:

In a 28-day study by the NTP, F344/N rats and B6C3F$_1$ mice were fed cresol isomers in the diet (DECOS). The values found for the NOAELs and LOAELs are summarised in Table 1 together with the critical toxic effects. A detailed description of the subchronic toxicity of the isomers is given in the appendix of the DECOS report (1998). For rats, the lowest NOAEL was 27 mg/kg bw (males) for the *m*-cresol : *p*-cresol mixture (60 : 40). For mice, no NOAEL could be determined because even the lowest tested *p*-cresol dose of 66 mg/kg bw increased the relative liver weights in the male animals.

There are several studies available, in which rats were exposed to cresol isomers orally for 13 weeks. Thus include a 13-week toxicity study by the NTP with application of the substances with the diet (DECOS 1998) and by gavage (DECOS 1998), a 13-week neurotoxicity study (DECOS 1998), and a 2-generation study (DECOS 1998). The values found for the NOAELs and LOAELs are summarised in Table 2 together with the critical toxic effects. A more detailed description of the chronic toxicity of the isomers and the mixtures is given in the DECOS report (1998). The studies revealed a NOAEL of all cresol isomers or their mixtures of 50 mg/kg bw for the rat.

In the 13 week feeding study by NTP with B6C3F$_1$ mice (DECOS 1998) the NOAEL for *o*-cresol was 496 mg/kg bw (female mice), for the mixture of *m*-cresol and *p*-cresol 402 mg/kg bw (male animals) and 923 mg/kg bw (female animals). For *o*-cresol administered to male mice, no NOAEL could be determined because even with the lowest tested dose of 199 mg/kg bw the relative liver weights of the male animals were increased.

2.6. Reproductive toxicity

In a 2-generation study with Sprague-Dawley rats, the NOAEL for parental animals was concluded to be 30 mg/kg bw and day (*o* -cresol and *p*-cresol) and <30 mg/kg bw (*m*-cresol), that for the progeny as 175 mg/kg bw (all isomers) (DECOS 1998).

Developmental toxicity studies with the three isomers were performed using rats and rabbits. The NOAELs for maternal and developmental toxicity are summarised in Table 3. NOAELs for maternal toxicity are higher than 100 mg/kg bw except for *p*-cresol in rabbits, for which the NOAEL was 50 mg/kg bw. The NOAELs for developmental effects are the same or higher than that for maternal toxicity with the exception of *o*-cresol in rabbits. In this experiment, there were some effects indicative of slight fetotoxicity (poorly ossified sternebrae, increased incidence of subepidermal haematomas on the head) in the high dose group (100 mg/kg bw) whereas this dose induced no maternal toxicity apart from some occational clinical signs (audible respiration 2/14, hypoactivity 1/14).

2.7. Genotoxicity

Genotoxicity studies in vitro and in vivo are summarised in Table 4. The results suggest that the isomers and their mixture are not mutagenic in Salmonella typhimurium, however, *o*-cresol, *p*-cresol and the 1:1:1 mixture showed genotoxic acitivity (chromosomal aberration and sister chromatid exchange) in some mammalian cell systems (CHO cells). In vivo, there is no evidence for a genotoxic activity (DECOS 1984; Greim 2000).

2.8. Carcinogenicity

No studies concerning the carcinogenicity of cresol isomers when administered alone or in mixtures of them were found (DECOS 1998). However, long-term carcinogenicity studies with *o*-cresol and a mixture of cresol isomers are planned by the NTP (Greim 2000).

The isomers and their mixtures may influence the carcinogenicity of other compounds. Especially *o*-cresol showed a potential tumour-promoting activity:

o-Cresol modified the carcinogenic effect of benzo[a]pyrene on the forestomach of mice. Simultaneous administration by gavage of >1 mg *o*-cresol plus 1 mg benzo[a]pyrene to female CC57Br mice, twice weekly, twenty times, increased the incidence, the multiplicity, and the degree of malignancy of forestomach epithelial tumours, and shortened latency (DECOS 1998).

After a single, initiating dose of 9,10-dimethyl-1,2-benzanthracene, the separate cresol isomers promoted papilloma growth in the skin of female Sutter mice when applied in benzene twice weekly for eleven weeks. Treatment resulted in relatively high mortality (Table 5). *o*-Cresol was most potent inducing an average number of papillomas per surviving mouse of 1.35 (*m*-cresol 0.93; *p*-cresol 0.55; see Table 5). No carcinoma were observed in any mouse. No papillomas were found in the benzene control group. In four out of five benzene control groups from parallel running experiments using other compounds, there were no papillomas either (Boutwell and Bosch 1959). To what extent the proliferation stimulus associated with the irritative effects of the cresol isomers had an influence on the promoting effects cannot be determined conclusively because in these studies details of skin damage caused by the cresol isomers are not given. However, there is also evidence of promoting effects which are independent of skin irritation (Greim 2000).

Human data

Local effects: A study carried out in Russia (Uzhdavini et al. 1972) considered 6 mg/m^3 (1.4 ppm) as the threshold concentration for the production of mucosal irritation by *o*-cresol (vapour/aerosol mixture) in humans. However, at this concentration, 8 out of 10 subjects complained of symptoms such as dryness, nasal constriction and throat irritation. Furthermore, neither the duration of exposure nor the composition (i.e. purity) of the compound were specified in the report (WHO 1995). Dermal exposure to cresols may result

in severe skin irritation (corrosion, burns) and dermatitis. The cresols are considered to be severe eye irritants as well (DECOS 1998)

Acute exposure: There are numerous case reports describing effects following intentional or accidental ingestion of cresols. These effects include irritation of mouth and throat, abdominal pain and vomiting, tachycardia and ventricular fibrillation, haemolytic anaemia, liver and kidney damage, facial paraesthesia, headache, dizziness, convulsion, coma, and death. In addition, (heavy) dermal exposure, due to spilling or immersing hands for hours produced effects on the central nervous system, liver, kidney, and vascular system, and was lethal (DECOS 1998).

Repeated exposure: No epidemiological studies or case reports on occupationally exposure to cresols were found containing adequate details on exposure levels, etc. NIOSH refers to reports from decades in which workers exposed to unknown concentrations of cresols in combination with unknown concentrations of other chemicals (formaldehyde, ammonia, phenols) suffered from nervous system and vascular disturbances (DECOS 1998).

Reproductive toxicity: Women in the former Soviet Union engaged in a manufacture of enamel-insulated wires or tricresylphosphate and occupational exposure to tricresol and other compounds as chlorobenzene and phosphorylchloride were reported to have menstrual disorders, hormonal disturbances, increased frequency of perinatal mortality, and increased abnormal development of newborns. However, no data on exposure levels, exposure duration or employment duration, presence of other compounds, control groups, etc. were presented (DECOS 1998).

Carcinogenicity: Based on its excretion in urine, endogenous *p*-cresol was concluded not to contribute significantly to the development of human bladder cancer or cancer of the large intestines (DECOS 1998). Two cases of multifocal bladder carcinoma (transitional cell carcinoma) were described after long-term exposure to cresol and a mixture of substances (Garrett 1975). Since no data for the exposure concentrations are available and since exposure was to a mixture of substances, a carcinogenic potential of the cresol isomers cannot be deduced from these case reports.

Recommendation

The systemic toxicity of the cresol isomers has been adequately studied in oral animal experiments, resulting in a NOAEL for rats of 50 mg/kg bw/day. However, hazard assessment based on oral studies is not appropriate because there are indications that local irritation is the critical effect of cresol vapours. Adequate inhalation studies are not available. In an inadequately documented study (Uzhdavini et al. 1972), *o*-cresol concentrations of 6 mg/m^3 (1.4 ml/m^3) led to irritation in man and *o*-cresol concentrations of 9 mg/m^3 (2.1 ml/m^3) led to irritation as well as morphological changes in the respiratory tissues of rats. There are no data available, to show what the no-effect concentration would be. The data base is therefore not sufficient for deriving scientifically based occupational exposure limits. However, the existing 8-hour TWA of 5 ppm (22 mg/m^3) seems to be too high.

From the data available, a weak genotoxic activity in vitro but no genotoxic activity in vivo was deduced. In initiation-promotion studies the cresol isomers reveal a promoting effect like that of phenol. Carcinogenicity studies are not available.

A "skin" notation was recommended as dermal absorption could contribute substantially to the total body burden.

Key Bibliography

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Table 1. NOAEL and LOAEL in rats and mice after administration of individual cresol isomers in the diet for 28 days (DECOS 1998)

Isomer	Sex	NOAEL (mg/kg bw)	LOAEL (mg/kg bw)	Effect
Rat				
o-cresol	M	87	266	increased relative liver weight
	F	271	881	increased relative liver weight
m-cresol	M	252	867	increased relative and absolute liver weights
	F	252	862	increased relative liver weight
p-cresol	M	87	256	bone marrow hypocellularity
	F	83	242	increased relative and absolute liver weights
m-cresol : *p*-cresol (60 : 40)	M	90	261	increased relative liver weight, histological changes in the thyroid gland
	F	27	95	increased relative and absolute liver weights
Mouse				
o-cresol	M	193	558	increased relative liver weight
	F	280	763	increased relative liver weight
m-cresol	M	193	521	increased relative liver and kidney weights
	F	<66	66	increased relative liver weight
p-cresol	M	163	469	increased relative kidney weight
	F	207	564	increased relative liver weight
m-cresol : *p*-cresol (60 : 40)	M	50	161	increased relative liver weight
	F	200	604	increased relative and absolute liver weights

Table 2. NOAEL and LOAEL from subchronic rat studies (DECOS 1998; modified)

Isomer	Study type, dose/concentration, strain	Sex	NOAEL (mg/kg bw)	LOAEL (mg/kg bw)	Effect	Reference (see DECOS 1998)
Rat						
o-cresol	13-week feeding study, F344 rats	M, F	250	510	increased relative and absolute liver weights	Die92
	13-week gavage study, SD rats	M, F	175	600	mortality, CNS depression	Die88a
	2-generation gavage study, SD rats	M, F	175	450	mortality, CNS depression	Tyl89
	13-week neutotoxicity gavage study, SD rats	M, F	175	450	clinical signs	TRL86
m-cresol	2-generation gavage study, SD rats	M, F	175	450	mortality, CNS depression	Nee89a
	13-week gavage study, SD rats	M	50	150	reduced body weight (gain)	Die88b
		F	150	450	clinical signs	
	13-week neutotoxicity gavage study, SD rats	M, F	150	450	clinical signs	TRL86
p-cresol	2-generation gavage study, SD rats	M, F	175	450	mortality, CNS depression	Nee89b
	13-week gavage study, SD rats	M, F	50	175	mild anaemia (F), increased total protein (M)	Die88c
	13-week neutotoxicity gavage study, SD rats	M, F	175	600	clinical signs	TRL86
m-cresol : *p*-cresol (60 : 40)	13-week feeding study, F344 rats	F	131	509	lengthened oestrus cycle; increased relative and absolute liver weights	Die92
		M	123	241	increased absolute liver weight	
Mouse						
o-cresol	13-week feeding study, B6C3F1 mice	F	496	935	increased relative liver weights	Die92
		M	--	199	increased relative liver weights	
m-cresol : *p*-cresol (60 : 40)	13-week feeding study, B6C3F1 mice	F	923	1623	decreased body weight; increased relative liver weight	Die92
		M	402	776	incresed relative and absolute liver weight	

Table 3. NOAEL for maternal and developmental toxicity in rats and rabbits

Species	Isomer	NOAEL maternal (mg/kg bw)	NOAEL developmental (mg/kg bw)	Refernce (see DECOS 1989)
Rat	*o*-cresol	175	175	Tyl88a
	m-cresol	175	≥450	Tyl88a
	p-cresol	175	175	Tyl88a
Rabbit	*o*-cresol	≥100	50	Tyl88b
	m-cresol	≥100	≥100	Tyl88b
	p-cresol	50	≥100	Tyl88b

Table 4. Genotoxicity of cresol isomers

Indicator organism (administration route)	End point	*o*-Cresol	*m*-Cresol	*p*-Cresol	Mixture (1:1:1)	References (see Greim 2000)
		Results with/without metabolic activation[1]				
in vitro						
Salmonella typhimurium	reversion	–/–	–/–	–/–	–/–	CTF 1980a, 1981a, Douglas *et al.* 1980, Florin *et al.* 1980, Haworth *et al.* 1983, NTP 1992, Pool and Lin 1982
rat hepatocytes	UDS[3]	–[2]			(+)[2]	CTF 1980d, 1981e
rat hepatocytes	UDS		n.d./–			CMA 1988a
human lymphocytes	UDS			n.d./(+)		Daugherty and Franks 1986
mouse lymphoma cells L5178Y-TK$^{+/-}$	forward mutation	–/–	–/–	–/–	+/(+)	CMA 1988b, CTF 1980b, 1981b
CHO cells	CA[4]	+/+	–/–	+/+		CMA 1988c
CHO cells	SCE[5]	+/+			+/+	CTF 1980c, 1981c
human fibroblasts	SCE	n.d./–	n.d./–	n.d./–		Cheng and Kligerman 1984
human lymphocytes	SCE	n.d./–	n.d./–	n.d./–		Jansson *et al.* 1986
in vivo						
Drosophila melanogaster	sex-linked recessive lethal mutations	–		–		CMA 1989a, 1989b
DBA/2 mice (i.p.)	SCE	–	–	–		Cheng and Kligerman 1984
ICR mice (oral)	CA (bone marrow)		–			CMA 1989c
ICR mice (oral)	dominant lethal test	–		–		CMA 1989d, 1989e

[1] – : negative results, + : positive results, (+) : weak positive results, n.d. : not determined
[2] not stated whether the tests were carried out with or without metabolic activation
[3] unscheduled DNA synthesis
[4] chromosomal aberrations
[5] sister chromatid exchange

Table 5. Tumour promoting effects of the cresol isomers and phenol (Boutwell and Bosch 1959)

Species: female Sutter mice, 27–29 animals per group
Initiation: dermal, one dose of 75 µg 9,10-dimethyl-1,2-benzanthracene (DMBA) in 25 µl solvent
Promotion: dermal, twice weekly, promoter in 25 µl benzene, treatment with the promoter for 6 weeks after application of the initiator

Initiation: 75 µg DMBA in 25 µl (solvent)	promoter in 25 µl benzene	Results after [number of weeks]	Surviving animals/ total number of treated animals	Surviving animals with papillomas [%]	Number of papillomas per animal	Surviving animals with carcinomas [%]
Exp. 1 (acetone)	–	12	12/12	0	0	0
(acetone)	20 % *o*-cresol (≅ 4.4 mg)	12	17/27	59	1.35	0
(acetone)	20 % *m*-cresol (≅ 4.4 mg)	12	14/29	50	0.9	0
(acetone)	20 % *p*-cresol (≅ 4.4 mg)	12	20/28	35	0.6	0
(acetone)	20 % phenol (≅ 5 mg)	12	22/27	64	1.5	0
Exp. 2 (benzene)	–	20	18/20	0	0	0
(benzene)	5.7 % *m*-cresol (≅ 1.25 mg)	20	17/20	24	0.2	0
(benzene)	5.7 % *p*-cresol (≅ 1.25 mg)	20	14/20	29	0.4	0
(benzene)	5 % phenol (≅ 1.25 mg)	20	13/19	31	0.5	8
(benzene)	10 % phenol (≅ 2.5 mg)	20	12/20	83	2.1	8