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Pulmonary Toxicity of Polyalkylene Glycols

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ECETOC Technical Report No. 55

PULMONARY TOXICITY
OF
POLYALKYLENE GLYCOLS

CONTENTS

SUMMARY

Polyalkylene glycols (polyglycols; PAG) are a group of polymeric chemicals with a wide range of physicochemical properties and applications. No significant adverse health effects arising from industrial experience over many years have been reported for these chemicals. PAG have low vapour pressures and no adverse effects have been reported following exposure to vapour atmospheres at ambient temperature.

Experimental animal studies involving a range of PAG have revealed, however, that inhalation of aerosols can, in some cases, lead to severe delayed toxic effects in the lung. A review of the data shows that these toxic effects are confined to two areas of PAG chemistry and differ only in severity of the responses seen. In acute toxicity studies certain butanol and water-initiated random 50:50 ethylene oxide-propylene oxide (EO-PO) copolymers of molecular weight 2,900 and greater induce significant toxic changes in the rat lung including congestion, haemorrhage, interstitial pneumonia and Type II pneumocyte hyperplasia; interstitial focal fibrosis occurs after longer exposure. In sub-acute toxicity studies similar though less severe changes are seen in the lung with 1,700 molecular weight copolymers of similar composition; certain block and reverse-block EO-PO copolymers of molecular weight 1,100 and greater show similar, though less severe changes in the lung.

Acute aerosol inhalation toxicity data on other PAG (diol-and triol-initiated polymers and copolymers and copolymers with different proportions of EO and PO) demonstrate that this pattern of lung toxicity is not general for PAG.

The underlying reasons for the apparent specificity in chemical composition responsible for the observed effects have not been demonstrated. Ultrastructural studies conducted after exposure of rats to random copolymers have suggested that the Type I pneumocytes lining the alveoli are the primary target cell. For random copolymers the available information points to the uptake of circulating unmetabolised copolymer into lung epithelial cells by an active transport mechanism.

In view of these findings, it is recommended that inhalation exposure to those PAG copolymers, shown to have adverse lung effects in animal studies, is adequately controlled where there is the possibility of aerosol generation in the workplace.

1. INTRODUCTION AND BACKGROUND

Polyalkylene glycols (polyglycols; PAG) are a diverse group of polymeric materials with a broad spectrum of uses. They vary from slightly viscous liquids to waxy solids and have been synthesised with a range of physico-chemical properties to meet particular performance requirements. PAG have a wide variety of uses including anti-foam agents, synthetic quenching agents, industrial lubricants, mould release agents and cosmetic oil substitutes; they also have pharmaceutical uses and are chemical intermediates (Rowe and Wolf, 1982).

Products in this chemical family vary considerably in molecular weight (MW), water solubility and viscosity; their properties determine their end-use applications (Klonne *et al*, 1987). The various products, manufactured by different producers, are marketed under a variety of trade names.

Because of the wide range of applications of these materials and their long (more than five decades) history of use, there has been extensive toxicological evaluation and industrial experience. In experimental animals, all of the materials have demonstrated low toxicity by the dermal and oral routes of exposure, little or no irritancy or sensitisation potential, no significant systemic effects except following high-dose, repeated exposures and no evidence of carcinogenic potential. In common with many other organic compounds, the inhalation of atmospheres formed from heated PAG produced adverse effects, because of thermal degradation leading to the formation of a range of noxious materials including ketones, aldehydes and acids (Donbrow, 1987). No indication of significant toxicity has been seen in experimental animals after inhalation of vapour produced at room temperature; the saturated vapour pressures for PAG are generally lower than 0.01 hPa (Rowe and Wolf, 1982; Ullmann, 1984; Klonne *et al* 1987). No significant adverse human experience has been reported (Rowe and Wolf, 1982).

The screening of butanol-initiated 50:50 random EO-PO copolymers of higher MW for effects of aerosol inhalation yielded unexpected results not seen following oral exposure; these data were first published by Klonne *et al* (1987). A large number of investigations aimed at understanding the nature of the toxic effect, delineating the type of polymers responsible and elucidating the mechanism of toxicity have subsequently been undertaken.

This Technical Report reviews the available information relevant to pulmonary toxicity and summarises the current state of knowledge. Section 2 briefly describes the synthesis and chemistry of the molecules concerned, Sections 3, 4, and 5 review the available studies on pulmonary toxicity and Section 6 reviews the studies carried out specifically to elucidate the suggested mechanisms for pulmonary toxicity. Finally, Section 7 provides an integrated discussion of the available data.

2. CHEMISTRY OF POLYALKYLENE GLYCOLS

2.1 SYNTHESIS

PAG are prepared by reacting alkylene oxides, normally EO or PO, with an active hydrogen-containing initiator, for example water, alcohols or amines. The reaction requires an alkali catalyst (frequently potassium hydroxide) and a temperature of about 100-150^{0}C. After the reaction, the catalyst is either neutralised by acidification or removed by filtration following the addition of a chemical, such as magnesium silicate, which will combine with the catalyst to form an insoluble product.

If two alkylene oxides are used, they can be fed sequentially (yielding block copolymers) or as a mixed feed (yielding random copolymers). Block copolymers may be "normal", i.e. a block of PO on the initiator followed by a terminal block of EO, or "reverse", an EO block on the initiator followed by a terminal block of PO.

In all cases, the final PAG is not a single compound but a mixture of polymer chains which have approximately a normal distribution around the desired MW. Impurities are mainly polyglycols, the MW depending on the stage in the alkoxylation when the impurity-initiator was formed.

2.2 SOURCES OF 'IMPURITIES' IN MIXED COPOLYMERS

The PAG used as synthetic lubricants have typically been random copolymers with a blend of EO and PO (normally 50:50 % weight basis) and a practical maximum MW of around 4,500. During synthesis the reactivity of the alkoxylate is reduced with increasing molecular weight, so that as the molecules build, competing side reactions become progressively more important. This can create different initiators from that originally present:

(i) ***Allyl alcohol derivatives***

Under the influence of temperature, basic conditions (alkaline catalyst), and in the presence of any PO alkoxylate, PO can rearrange to form allyl alcohol which then acts as an initiator for further reaction with the alkylene oxides.

$$CH_3\text{-}CH\text{-}CH_2 \rightarrow CH_2{=}CH\text{-}CH_2OH$$
$$\quad\quad\ \backslash\ /$$
$$\quad\quad\ \ O$$

The average MW of the allyl alcohol alkoxylate is always lower than the average parent alkoxylate.

(ii) ***Propenyl alcohol derivatives***

At high temperatures under alkaline conditions, allyl(2-propenyl) alcohol alkoxylate (formed as above) can rearrange to 1-propenyl alcohol alkoxylate.

$$CH_2=CH-CH_2-O-(EO-PO)-H \rightarrow CH_3-CH=CH-O-(EO-PO)-H$$

(iii) ***Formation of diol alkoxylate***

Contamination by water will lead to the formation of diol alkoxylate which will grow at twice the rate of the parent monoalkoxylate, and thus can rapidly become a major impurity in the final product. The amount of water present may be reduced by distillation prior to alkoxylation.

$$H-O-H + 2(EO-PO) \rightarrow H-(EO-PO)-O-(EO-PO)-H$$

This water may come from three sources :

- Water in initiator, oxides or catalyst.
  The initiator and the alkylene oxides may contain small quantities of water, whilst the catalyst is often added diluted in water.

- Water from the reaction of catalyst with initiator.
  The alcohol reacts with the alkali catalyst, forming an alkoxide with the release of water:
  $$ROH + KOH \rightarrow ROK + H_2O$$

- Water from the degradation of alkoxylate.
  The terminal group of the alkoxylate may dehydrate (releasing water) or degrade releasing a glycol).

2.3 VARIATION IN COMPOSITION OF 50:50 RANDOM COPOLYMERS WITH VARYING MOLECULAR WEIGHTS

Irrespective of the original initiator, the same range of impurities is produced during any alkoxylation reaction. Thus 4 main groups will be present in the reaction mixture of all copolymers:

- the parent alkoxylate;
- allyl alcohol alkoxylates;
- propenyl alcohol alkoxylates;
- diol alkoxylates.

As an example, the main components of the PAG produced by reaction of butanol (as initiator) with a 50:50 % weight random feed of EO-PO can be summarised as follows:

a) Butanol alkoxylate (Bu-O-(EO-PO)-H)
b) Allyl alcohol alkoxylate (Al-O-(EO-PO)-H)
c) Propenyl alcohol alkoxylate (Pr-O-(EO-PO)-H)
d) Diol alkoxylate (H-(EO-PO)-O-(EO-PO)-H)

(The products b) c) and d) are not unique to butanol-initiated PAG).

The relative abundance of the parent alkoxylate, monol and diol alkoxylates in the final PAG varies with MW (see Section 2.2 above for the explanation of a) to d))

(i) Low MW PAG (av. MW < 1,300)
There will typically be more than 95% weight butanol alkoxlate a), with very low quantities of compounds b), c) and d).
(ii) Medium MW PAG (av. MW 1,300-2,600)
Compound a) will decrease to about 90-95%, whilst d) will increase to about 15%. Compounds b) and c) will begin to appear.
(iii) High MW PAG (av. MW > 2,600)
Compound a) will be present at about 60-90 %, the other products, b), c) and d) will also be present at high concentrations.

A typical analysis of various butanol-initiated polyalkylene glycols is shown in Table 1.
As the MW of the PAG increases, so does the average MW of the individual impurities. Increasing MW leads to formation of new initiators (diol and unsaturated monols). As the average MW of the copolymer increases, the unsaturated products and the diol alkoxylate impurities achieve a significant concentration.

The number of possible by-products in any organic chemical reaction can be large, due to side reactions and the presence of impurities in the reactants. The reactions discussed above are only those that are well known.

Table 1: Typical Analysis of Butanol-Initiated PAG According to Average MW

PAG Av. MW	% Butanol Alkoxylate	% Monol Alkoxylate	% Diol Alkoxylate
< 1,300	99	<1	1
1,300-2,000	97-99	<1	2
2,000-2,600	90-95	1-2	3-10
2,600-3,300	80-90	3-7	10-20
3,300-4,000	60-80	10-20	15-25

2.4 COMPOSITION OF POLYALKYLENE GLYCOLS

The PAG referred to in this report represent a range of MW having a normal distribution around the mean. Details of the copolymers and polymers for which inhalation data are available, as discussed in this report, are presented in Table 2.

Table 2: PAG Studied for Inhalation Toxicity

Initiator	Name	Av. MW	% EO-PO	Type
MONOLS				
Butanol	UCON*50-HB-170	730	50:50	Random
	UCON*50-HB-260	970	50:50	Random
	UCON*50-HB-660	1,700	50:50	Random
	UCON*50-HB-2000	2,900	50:50	Random
	UCON*50-HB-5100	4,000	50:50	Random
	UCON*50-HB-5100R**	4,000	50:50	Random
	ICI Copolymer	4,000	50:50	Random
	Pluracol* W-5100	4,200	50:50	Random
	ICI Copolymer	4,500	50:50	Random
Octylphenol	TRITON*X-100	647	100% EO	Homopolymer
DIOLS				
Water (or diethylene glycol, or dipropylene glycol)	UCON*50-H-5100**	4,000	50:50	Random
	UCON*75-H-1400	2,200	75:25	Random
	UCON*75-H-9500	Not available	75:25	Random
	UCON*75-H-380,000	»12,000	75:25	Random
	Pluronic*L31	1,100	10:90	Block
	Pluronic*L64	2,900	40:60	Block
	Pluronic*L81	2,750	10:90	Block
	ICI Block Copolymer A	4,000	30:70	Block
	Pluronic*P84	4,200	40:60	Block
	Pluronic*L122	5,000	20:80	Block
	ICI Block Copolymer B	12,000	80:20	Block
	Pluronic*17R1	1,900	10:90	Reverse Block
	Pluronic*31R1	3,700	15:85	Reverse block
	Polyethylene glycol 200	200	100% EO	Homopolymer
	Polyethylene glycol 3350	3,350	100% EO	Homopolymer
TRIOLS				
Glycerol	Polyglycol 15-200	2,600	50:50	Random

* Trade Name
** Polymer not commercially available

3. PULMONARY TOXICITY OF MONOL-INITIATED POLYMERS (EXPOSURE TO AEROSOLS)

3.1 BUTANOL-INITIATED POLYMERS

3.1.1 50:50 Ethylene Oxide, Propylene Oxide Random Copolymers

UCON 50-HB-170 (av. MW 730)

Acute inhalation toxicity (Appendix A)

Groups of 6 male Crl:CD(SD)BR rats were exposed (nose only) to aerosol concentrations of 410, 730, 2,200, 4,200 or 5,100 mg UCON 50-HB-170/m^3 for 4 hours. Clinical signs during exposure were confined to red nasal and/or ocular discharge. Minimal body-weight loss was recorded one day after exposure, followed by normal weight gain thereafter. The approximate lethal concentration (ALC) defined as the lowest exposure concentration resulting in mortality for UCON 50-HB-170 exceeded 5,100 mg/m^3 (DuPont, 1985a).

UCON 50-HB-260 (av. MW 970)

Acute inhalation toxicity (Appendix A)

Groups of 5 male and 5 female Sprague-Dawley rats were exposed (whole-body) to aerosol concentrations of 3,870, 4,430 or 4,920 mg UCON 50-HB-260/m^3 for 4 hours. Clinical signs during exposure included hypothermia, red periocular encrustation and unkempt (wet, oily) appearance. Deaths were recorded 4-11 days after exposure at the highest exposure concentration; signs of respiratory irritation, ataxia, decreased motor activity and slow reflexes were reported amongst animals that died. Body-weight loss or reduced weight gain was recorded at the two highest exposure concentrations. Post-mortem examination of the animals that died revealed dark red discoloration of the lungs; no macroscopic changes were seen in animals killed 14 days after exposure. The acute inhalation LC_{50} value was calculated to be 4,770 mg/m^3 (95% confidence limits 4,260-5,350 mg/m^3) (Union Carbide, 1988a).

Sub-acute inhalation toxicity (Appendix C)

Groups of 10 or 20 Fischer rats per sex were exposed (whole-body) for 6h/d, 5d/w for 9 exposures over 11 days to aerosol concentrations of 5.0, 52 or 512 mg UCON 50-HB-260/m^3. Ten control animals and 10 animals exposed to 512 mg/m^3 were maintained for a 6-week recovery period. The principal exposure-related effects were decreased body-weight gain in animals exposed to 52 or 512 mg/m^3 and increased white blood cell counts and elevated absolute kidney weights after exposure to 512 mg/m^3. Gross post-mortem examination confirmed clinical evidence of minor ocular/nasal irritation, effects being noted mainly in animals exposed to 512 mg/m^3. There were no exposure-related effects observed in the 512 mg/m^3 groups sacrificed at the end of the 6-week recovery period. No histopathological lesions were observed in the 8 organs evaluated in this study, including lung and kidney (Union Carbide, 1989a; Tyler *et al*, 1990). The histopathological no observed adverse effect level (NOAEL) was determined in a subsequent review of the lung slides of this study. The NOAEL for UCON 50-HB-260 was ~ 500 mg/m^3 (Lewis, 1995).

UCON 50-HB-660 (av. MW 1,700)

Acute inhalation toxicity (Appendix A)

Groups of 5 male Wistar rats were exposed (whole-body) to aerosol concentrations of 2,590, 3,860 or 5,230 mg UCON 50-HB-660/m^3 for 4 hours; a group of 5 female rats was similarly exposed to an aerosol concentration of 5,230 mg 50-HB-660/m^3. No clinical signs were recorded during exposure. On removal from the chambers, increased respiration rate and hypoactivity were recorded in the rats at the highest exposure concentration. In this group, 4/5 males and 1/5 females died after 4-5 days; increases in respiratory rate and locomotor activity were recorded in some animals prior to their death. Post-mortem examination of the animals that died revealed mottled lungs and livers. The remainder of the animals were killed 14 days after exposure, when no exposure-related macroscopic changes were evident. Acute inhalation LC50 values (with 95% confidence limits) were 4,670 mg/m3 (4,090 - 5,320 mg/m3) in males and > 5,230 mg/m^3 in females (Klonne *et al*, 1987).

In a study of acute inhalation employing a nose-only exposure system, groups of 6 male Crl:CD(SD)BR rats were exposed to aerosol concentrations of 1,200, 2,900, 4,100 or 5,400 mg UCON 50-HB-660/m^3 for 4 hours. Clinical signs (red nasal and ocular discharge) were confined to rats exposed to 2,900 mg/m^3 and above. Exposure-related mortalities occurred by the 4th day post-exposure in the 2,900 mg/m^3 group (1/6), the group exposed to 4,100 (1/6) and in those animals exposed to 5,400 mg/m^3 (5/6). The ALC for UCON 50-HB-660 was 2,900 mg/m^3 (acute LC_{50} value approximately 4,500 mg/m^3) (DuPont, 1985b).

Sub-acute inhalation toxicity (Appendix C)

Groups of 10 or 20 Fischer 344 rats were exposed (whole-body) for 6 h/d, for 9 exposures over an 11-day period to aerosol concentrations of 0, 504, 982 or 2,460 mg UCON 50-HB-660/m^3. All rats exposed to 2,460 mg/m^3 died. Signs of ocular and nasal irritation, respiratory difficulty and reduced body weight and/or body-weight gain were observed in all treated groups. Many of the haematology, serum chemistry and urinary parameters analysed were abnormal in animals exposed to 504 or 982 mg/m^3. At the time of post-mortem examination, pulmonary congestion and an elevation in lung weights (absolute and relative) was also observed in these 2 exposure groups. Of the organs evaluated histopathologically, lesions were found only in the lung; these included interstitial pneumonitis, bronchoalveolar cell hyperplasia and intra-alveolar macrophage infiltration. The severity of these lesions was concentration related. The pattern of toxic responses seen following repeated inhalation exposure to UCON 50-HB-660 indicated that the effects were cumulative (Union Carbide, 1988b, Klonne *et al*, 1989a). The histopathological lowest observed adverse effect level (LOAEL) was determined in a subsequent review of the lung slides of this study. The LOAEL for UCON 50-HB-660 was ~ 500 mg/m^3 (Lewis, 1995).

In a further study, groups of 10 or 20 Fischer 344 rats were exposed (whole-body) for 6h/d, for 9 exposures over 11 days to aerosol concentrations of 0, 4.8, 50.6, 97.7 or 492 mg UCON 50-HB-660/m^3. Ten control animals and 10 animals exposed to 492 mg/m^3 were maintained for a 6-week recovery period. All rats survived and clinical signs (unkempt appearance, urinogenital wetness, swollen periocular tissue, rapid respiration and perinasal encrustation) were confined to rats exposed to 492 mg/m^3. Decreased body weight and weight gain were recorded in this group, whilst transient reduction in weight gain was seen in female rats exposed to 97.7 mg/m^3. Haematology and blood chemistry changes were recorded in rats, exposed to aerosol concentrations of 50.6 mg/m^3 or greater, at the end of the treatment period; the toxicological significance of the changes is uncertain. At autopsy, treatment-related increases in both absolute and body weight-related kidney and lung weights were recorded. Histopathological changes were confined to the lungs of treated animals, where observations included minimal-to-moderate intra-alveolar cellular debris and foci of interstitial pneumonitis (at 492 mg/m^3) and alveolar macrophage infiltration (at 50.6 mg/m^3 and above). All lung damage had resolved by the end of the 6-week recovery period (Union Carbide, 1991).

UCON 50-HB-2000 (av. MW 2,900)

Acute inhalation toxicity (Appendix A)

Groups of 5 male and 5 female Wistar rats were exposed (whole-body) to aerosol concentrations of 103, 412 or 992 mg UCON 50-HB-2000/m^3 for 4 hours (Klonne *et al*, 1987). No clinical signs were recorded during exposure. Deaths were recorded 2-5 days after exposure at the two highest exposure concentrations (412 mg/m^3 6/10; 992 mg/m^3 10/10). Slight increases in respiratory rate and locomotor activity were recorded in some animals prior to their death. Post-mortem examination revealed mottled lungs and livers. No exposure-related macroscopic changes were seen in the remainder of the animals, which were killed 14 days after exposure. The acute inhalation LC_{50} value was calculated to be 330 mg/m^3 (95% confidence limits 227-480 mg/m^3).

In an acute inhalation study employing a nose-only exposure system, groups of 6 male Crl:CD(SD)BR rats were exposed to aerosol concentrations of 300, 390, 470, 800 or 1,900 mg UCON 50-HB-2000/m^3 for 4 hours (DuPont, 1986a). During or immediately following exposure, rats in all groups had red nasal or ocular discharge. Exposure-related mortalities occurred between 2 and 5 days after exposure: 3 rats died after exposure at 390 mg/m^3, along with all animals exposed at higher concentrations. Slight weight loss was recorded in all rats during the first 5 days after exposure. Animals that died continued to lose weight until their death. Clinical signs recorded prior to death included laboured and noisy breathing, hunched posture and brown/red nasal discharge. The ALC for UCON 50-HB-2000 was 390 mg/m^3 (acute LC_{50} value approximately 400 mg/m^3).

Sub-acute inhalation toxicity (Appendix C)

In a study designed to evaluate the effects of inhalation of aerosols of a range of PAG (Warheit *et al*, 1995), a group of male Crl:CD(SD)BR rats was exposed (nose-only) to an aerosol concentration of 42.3 mg UCON 50-HB-2000/m^3, 6h/d, for 3 consecutive days. Sub-groups of 3 or 4 animals were subject to bronchoalveolar lavage procedure 0, 2 or 7 days, one month or 3 months after the final exposure; the lavage fluid was examined for cell count and viability, differential cell count, biochemistry (enzymes and protein), macrophage cell culture and phagocytosis assay (including Scanning Electron Microscopy of cells; SEM). Further sub-groups of 4 animals were used for pulmonary cell-labelling investigations (5-bromo-2-deoxyuridine labelling followed by perfusion fixation) immediately after the third exposure and 7 days later; the animals killed after 7 days were also used for histopathological evaluation. Control animals were exposed to air only.

One rat died within 8 days of the final exposure; at autopsy 2 days after exposure, the lungs of test animals appeared oedematous. Lung weights were correspondingly increased at this time. Evaluation of the bronchoalveolar lavage fluid revealed increased cell numbers, particularly one month after exposure;

the differential counts indicated transient pulmonary inflammation. The results of biochemical analysis of the lavage fluid were consistent with this effect; slight increases in protein and enzymes were recorded. Cell-labelling investigations revealed substantial labelling of the terminal bronchiolar cells immediately after the final exposure, with no differences from controls 7 days later. Histopathological evaluation of the lungs 7 days after the final exposure revealed only occasional and very slight areas of inflammation which were not regarded as biologically significant.

In a separate study, groups of 10 male Sprague-Dawley rats were exposed (whole-body) to an aerosol concentration of 103 mg UCON 50-HB-2000/m^3 6 h/d, for 9 days over an 11-day period. Lethargy, soft stools and prolapsed penis were observed during and after exposure. Six of the 10 test animals died after 3 exposures and surviving animals were sacrificed at the end of the first exposure week. Statistically-significant depression of body weight was observed in treated animals up to the time of sacrifice and at post-mortem examination their lung weight was elevated. Macroscopic examination of animals that died prior to termination revealed congestion, consolidation and red discoloration of the lungs. Treatment-related pulmonary consolidation was also detected in all animals sacrificed at the end of the first exposure week. Histopathological, treatment-related changes occurred largely in the alveoli and to a lesser extent in the terminal airways. There was moderate to severe multifocal or more-generalised alveolar inflammation, with a range of alveolar changes including varying degrees of hyperaemia and intra-alveolar oedema, haemorrhage, fibrin deposition and inflammatory cellular exudates (mostly alveolar macrophages and neutrophils). Areas of intense Type II pneumocyte hyperplasia, foci of alveolar organisation of exudates (pre-fibrotic changes) and thickened, hypercellular alveolar interstices were also seen. The cause of death was attributed to alveolitis, with pulmonary oedema (Ulrich *et al*, 1992).

UCON 50-HB-5100 (av. MW 4000)

Acute inhalation toxicity (Appendices A and B)

Groups of 5 male and 5 female Wistar rats were exposed (whole-body) to aerosol concentrations of 94, 116 or 940 mg UCON 50-HB-5l00/m^3 for 4 hours (Klonne *et al*, 1987). No clinical signs occurred during exposure. Animals died after 3-5 days in all groups (6/10 at 94 mg/m^3 and 10/10 at 940 mg/m^3); slight increases in respiratory rate and locomotor activity were recorded in some animals prior to death. Post-mortem examination of the animals that died revealed mottled lungs and livers; no exposure-related macroscopic changes were seen in the animals killed 14 days after exposure. The acute inhalation LC_{50} value was calculated to be 106 mg/m^3 (95% confidence limits 45-245 mg/m3).

In a study designed to evaluate the effects of acute inhalation of aerosols of a range of PAG (ICI, 1992), groups of 12 male Hsd/Ola (Wistar) rats were exposed to a target aerosol concentration of 75 mg UCON 50-HB-5100/m^3 for 2, 4 or 6 hours. The measured concentrations (in terms of exposure) were equivalent

to 4 hours exposure at concentrations of 36.3, 74.4 or 113.3 mg/m^3 UCON 50-HB-5l00. Control animals were exposed to air alone. The pattern of clinical effects was consistent with the results of previous studies. Toxicity was delayed; at day 2 no significant effects were noted on histopathological examination of the lungs or on the cell or protein content or the γ-glutamyl transferase activity of lung lavage fluid. However, by day 4, one animal exposed to 74.4 mg/m^3 died and the effects were such that, had the study not been terminated early, a median lethal concentration consistent with that established by Klonne *et al* (1987) would have been observed. Histopathological examination of lungs of surviving animals showed oedematous change combined with a strong inflammatory component. These findings were supported by the generalised protein and enzyme leakage and the concentration-related elevation and diversity of free cell types detected in lavage fluid.

In a study of acute inhalation employing a nose-only exposure system, groups of 6 male Crl:CD(SD)BR rats were exposed to aerosol concentrations of 61, 92, 140 or 210 mg UCON 50-HB-5100/m^3 for 4 hours (DuPont, 1984). Animals exhibited dose-dependent, slight-to-severe weight loss for up to 7 days. Red nasal and ocular discharges were observed 3-4 days post-exposure. Deaths were recorded 4-5 days after exposure in 1/6 animals receiving 61 mg/m^3 and 3/6 animals exposed to 92 mg/m^3. Deaths occurred after 3-5 days in all animals of the 140 mg/m^3 group and after 2-4 days in all animals of the 210 mg/m^3 group. The ALC for UCON 50-HB-5100 was 67 mg/m^3 (acute LC_{50} value approximately 100 mg/m^3). In a parallel study, rats were exposed to 230 mg UCON 50-HB-5100/m^3 for 4 hours and sacrificed 2 days after exposure. Histopathological examination revealed pulmonary oedema and haemorrhage, marked interstitial oedema, leucocytosis in the alveolar capillaries and focal leucocytic alveolar infiltration.

Further investigations of acute inhalation toxicity were undertaken by Hoffmann *et al* (1991) in a study involving several animal species (Appendices A and B). Groups of 10 male Sprague-Dawley rats, Swiss albino mice, Golden Syrian hamsters and Hartley albino guinea pigs were exposed (whole-body) to 54, 100, 200 or 500 mg/m^3 UCON 50-HB-5100 for 4 hours. Groups of 2 male Beagle dogs were similarly exposed to 52, 91, 310 or 450 mg/m^3 UCON 50-HB-5100. After exposure, animals were maintained for a 14-day observation period. No compound-related clinical effects were observed in any test animal during or immediately after exposure. During the post-exposure period emaciation, hypothermia, nasal discharge, laboured breathing, rales and ano-genital staining occurred, largely in the rodent species. Surviving animals generally showed recovery prior to sacrifice. Deaths occurred 3-9 days after exposure. The numbers of animals dying when exposed to 54, 100, 200 or 500 mg/m^3 UCON 50-HB-5100, were respectively: rats 0/10, 9/10, 3/10 and 10/10; mice 0/10, 2/10, 8/10 and 10/10; hamsters 0/10, 0/10, 0/10 and 5/10; guinea pigs 0/10, 0/10, 3/10 and 8/10. All dogs survived.

Dose-related body-weight loss was observed in the rodents during the first week after exposure; the surviving animals showed a recovery during the second week. There were no effects on dog body weights. Terminal lung weights were elevated at all exposure concentrations in rats, mice and hamsters

and in guinea pigs at 100 mg/m^3 and above. Lung weights in dogs were increased following exposure at 450 mg/m^3 only.

Pulmonary red discoloration, oedema, emphysema and surface irregularities were the most frequently observed gross post-mortem findings. These were the most evident in animals dying at the 3 highest exposure concentrations. Microscopic examination of the lungs showed acute congestion, oedema and haemorrhage accompanied in some cases by acute interstitial inflammatory change; these changes were considered to be the major factor causing death. The surviving animals of all species showed no treatment-related changes. No treatment-related histopathological changes were recorded in dogs exposed up to 450 mg/m^3.

The 4-hour LC_{50} values were calculated to be 147 mg/m^3 (rats), 174 mg/m^3 (mice), 293 mg/m^3 (guinea pigs) and 511 mg/m^3 (hamsters). The dog LC_{50} was > 450 mg/m^3 (Hoffman *et al*, 1991).

Sub-acute inhalation toxicity (Appendix C)

In a study designed to evaluate the effects of inhalation of aerosols of a range of PAG (Warheit *et al*, 1995), a group of male Crl:CD(SD)BR rats was exposed (nose only) to an aerosol concentration of 22.1 mg UCON 50-HB-5100/m^3, 6 h/d, for 3 consecutive days. Five sub-groups of 3 or 4 animals were subject to a bronchoalveolar lavage procedure 0, 2 or 7 days, one month or 3 months after the final exposure; the lavage fluid was examined for cell count and viability, differential cell count, biochemistry (enzymes and protein), macrophage cell culture and phagocytosis assay (including SEM). Two further sub-groups of 4 animals were used for pulmonary cell labelling investigations (5-bromo-2-deoxyuridine labelling followed by perfusion fixation) immediately after the third exposure and 7 days later; the animals killed after 7 days were also used for histopathological evaluation. Control animals were exposed to air only.

One rat died within 7 days of receiving 3 exposures. The authors reported that within 2 days, the lungs of rats exposed to UCON 50-HB-5100 were oedematous, and lung weights were correspondingly increased. Evaluation of the bronchoalveolar lavage fluid revealed increased cell numbers at all sampling periods up to and including one month after exposure; the differential counts indicated transient pulmonary inflammation. The results of biochemical analysis of the lavage fluid were consistent with this effect; substantial increases in protein and enzymes were recorded. Cell-labelling investigations revealed evidence of labelling of the terminal bronchiolar cells immediately after the final exposure, with no differences from controls 7 days later. Histopathological evaluation of the lungs 7 days after the final exposure revealed evidence of a localised and minimal chronic inflammatory response, with corresponding septal thickening.

In a separate study, groups of 10 male and 10 female Fischer 344 rats were exposed (whole-body) to aerosol concentrations of 0, 4.8, 25.5 or 49.5 mg UCON 50-HB-5100/m^3, 6 h/d, for a total of 9 exposures

during an 11-day period (Klonne *et al*, 1987). A further 10 animals of each sex exposed to either 0 or 49.5 mg 50-HB-5100/m^3 were maintained for a 2-week post-exposure recovery period before termination. During the first week of study, urinogenital wetness occurred in some females at the highest exposure concentration; animals of both sexes had an unkempt appearance and nasal discharge after 5 exposures. Mean body-weight gain was also reduced at the highest exposure concentration through the treatment and recovery periods. Weight gain was affected to a lesser extent in the intermediate group during the period of exposure and was reduced in male rats at the lowest exposure concentration by the end of the period of exposure. Urine samples collected prior to termination revealed no inter-group differences, whilst treatment-related effects on blood chemistry (decreased serum albumin and globulin concentrations and increased alanine aminotransferase activity) and haematology (increased number of neutrophils and eosinophils) were largely confined to female rats at the highest exposure concentration. All inter-group differences had resolved by the end of the recovery period. At post-mortem examination, lung weights were significantly increased in all treatment groups; macroscopic examination revealed irregular red foci in the lungs of rats in the middle and high concentration groups. Similar changes were evident in the recovery group animals exposed to 49.5 mg/m^3. Histopathological examination of the lungs revealed congestion and areas of haemorrhage between the pulmonary capillaries and the epithelial cells of the alveoli. Mild-to-moderate necrosis and exfoliation of alveolar lining cells and an increased number of macrophages phagocytosing debris within the alveolar spaces were evident. Hyperplasia of Type II pneumocytes, perivascular clusters of neutrophils around small pulmonary vessels, areas of interstitial pneumonia and tracheitis were also observed. The severity of pulmonary lesions in treated animals was considerably reduced by the end of the recovery period. The histopathological NOAEL and LOAEL were determined in a subsequent review of the lung slides of this study. The NOAEL was < 5mg/m^3 and the LOAEL ~ 5 mg/m^3 (Lewis, 1995).

In a further study, groups of 20 male Fischer 344 rats were exposed (whole-body) to concentrations of 0, 0.9 or 5 mg UCON 50-HB-5100/m^3, 6 h/d for a total of 9 exposures during an 11-day period (Klonne *et al*, 1988). Ten rats from each group were killed after 9 exposures, whilst the remainder were killed after a 4-week recovery period during which they were not further exposed. No exposure-related clinical signs were recorded and all animals survived with no clear effect on body-weight gain. Lung weights were significantly increased at termination after 9 exposures at the highest exposure concentration; a marginal increase was evident at the end of the recovery period. At autopsy, pulmonary congestion and small haemorrhagic foci scattered throughout the lung parenchyma were seen. Lesions were more numerous at the highest exposure concentration, but were also seen at the lower exposure concentration. At the end of the recovery period, tan coloured foci were seen on the lungs. Histopathological examination revealed a concentration-related incidence of multifocal haemorrhage with scattered histiocytic infiltrates. Type II pneumocyte hyperplasia, suggesting that alveolar cell necrosis had occurred, was only seen at the higher exposure concentration; other histopathological changes were limited to multifocal haemorrhage with alveolar macrophage infiltration, and their incidence and severity were concentration-related.

In a study designed to evaluate the inhalation toxicity of aerosols of a range of PAG, a group of animals exposed to UCON 50-HB-5100 was included as a positive control (Ulrich *et al*, 1992). This group of 10 male Sprague-Dawley rats was scheduled to be exposed to an aerosol concentration of 55 mg/m^3, for 6h/d, for a total of 9 exposures over 11 days. However after 3 exposures, 9/10 rats had died and the surviving animal was killed after 5 exposures. At post-mortem examination, animals that died had congestion, consolidation and red discoloration of the lungs; consolidation was also recorded in the animal killed after 5 exposures. Lung weights were increased compared to control values. Histopathological examination confirmed the presence of moderate-to-severe alveolitis (including intra-alveolar oedema, haemorrhage and fibrin deposition and areas of Type II pneumocyte hyperplasia).

Sub-chronic inhalation toxicity (Appendix D)

Groups of 20 male and 20 female Fischer 344 rats were exposed (whole-body) to aerosol concentrations of 0, 0.3, 1.1 or 5.2 mg UCON 50-HB-5100/m^3, 6 h/d, 5 d/w for 13 weeks (Klonne *et al*, 1988). Ten animals of each sex from each group were killed after 13 weeks and the remainder after a 5-week recovery period during which they were not further exposed. No exposure-related clinical signs were recorded during the study. Body-weight gain was slightly reduced in male rats at the highest concentration during the period of exposure and was less than that of controls at the end of the recovery period. Haematological examination after 13 weeks' exposure revealed only an increased number of neutrophils in male rats at the highest concentration and in female rats at the intermediate concentration; no inter-group differences were seen at the end of the recovery period. No effects of exposure were seen on blood chemistry, urine chemistry or ophthalmoscopy at any time. At post-mortem examination after 13 weeks' exposure, lung weights were increased in a concentration-related manner in all test groups. At the end of the 5-week recovery period, there was still clear evidence of increased lung weight in most treated groups. Grey or tan foci were seen on the lungs of animals from all test groups, both at the end of the exposure period and after the recovery period. Multifocal petechial haemorrhages of the lungs were seen at the highest exposure concentration after 13 weeks. Histopathological examination revealed haemorrhage and interstitial pneumonia (1.1 and 5.2 mg/m3 groups only), alveolar macrophage infiltration and focal or multifocal fibrosis (all groups). Lesions at the lowest exposure concentration were described as minimal in severity and focal in distribution. At the two highest atmosphere concentrations there was little reduction in the severity or incidence of lung lesions after the recovery period. In rats at the lowest exposure concentration (0.3 mg/m^3), alveolar macrophage infiltration was reduced during the recovery period but interstitial fibrosis was still evident.

ICI Copolymer (av. MW 4,000)

Acute inhalation toxicity (Appendix A)

Groups of 7 male Hsd/Ola (Wistar) rats were exposed to a target aerosol concentration of 75 mg ICI Copolymer/m^3 for 2 or 6 hours, equivalent (in terms of exposure) to 4-hour exposures to concentrations of 39.8 or 115.7 mg copolymer/m^3 (ICI, 1992). Exposure resulted in a similar pattern of events to that observed following exposure to UCON 50-HB-5100 at similar concentrations (Klonne *et al*, 1987). Death was delayed and the nature of lung damage (assessed both histopathologically and biochemically) was similar. Animals were sacrificed on day 4; body-weight losses were recorded prior to death.

Pluracol W-5100 (av. MW 4,200)

Acute inhalation toxicity (Appendix A)

Groups of 6 male Crl:CD(SC)BR rats were exposed (nose-only) to aerosol concentrations of 91, 92, 130, 200 or 360 mg Pluracol W- 5100/m^3 for 4 hours (DuPont, 1984). There was dose-dependent, slight-severe weight loss for up to 6 days. The majority of clinical signs (red nasal/ocular discharge) were noted 3-4 days post-exposure. Deaths were recorded on day 4 in 2/6 animals exposed to 92 mg/m^3, on day 5 in 1/6 rats of the 130 mg/m^3 group and on days 3-5 in 6/6 animals in exposure groups 200 and 360 mg/m^3. The ALC for Pluracol W-5100 was 92 mg/m^3 (acute LC_{50} value approximately 150 mg/m^3).

ICI Copolymer (av. MW 4,500)

Acute inhalation toxicity (Appendix A)

Groups of 7 male Hsd/Ola (Wistar) rats were exposed to a target aerosol concentration of 75 mg ICI Copolymer/m^3 for 2-6 hours, equivalent (in terms of exposure) to 4-hour exposures to concentrations of 37.8 or 116 mg copolymer/m^3 (ICI, 1992). Exposure resulted in a very similar pattern of events to that observed following exposure to UCON 50-HB-5100 at similar concentrations (Klonne *et al*, 1987). Mortalities were delayed and the nature of lung damage (assessed both histopathologically and biochemically) was similar. Animals were sacrificed on day 4; body-weight losses were recorded prior to death.

3.2 OCTYLPHENOL-INITIATED POLYMERS

3.2.1 100% Ethylene Oxide Polymers

Polyethylene Glycol p-Isooctylphenol Ether (TRITON X-100) (av. MW 647)

Acute inhalation/instillation study (Appendix B)

Dose-response studies were conducted with Syrian hamsters exposed to TRITON X-l 00 by inhalation or by a form of bronchopulmonary lavage (Damon *et al*, 1982). For the inhalation studies, animals were exposed to a single concentration of the test material for varying times to give the desired lung burden of the test material. Initial lung burden was calculated from the regional efficiency of deposition of aerosol particles of the size range in the test atmosphere and the minute volume of the test animals. For the lavage exposures, lung burden was calculated from the retention of tritiated TRITON X-100 in the lung. The hamsters were exposed (nose-only) to an aerosol of TRITON X-100, prepared from an ethanolic solution, at a concentration of 3,000 mg/m^3; appropriate ethanol controls were included in the study design. Groups of 10 hamsters were removed from exposure when they had received initial respiratory tract burdens ranging from 800-3,100 μg. Lavage was carried out with concentrations of TRITON X-100 ranging from 0.01-0.1% in isotonic saline, resulting in initial lung burdens of 300-3,200 μg. The LD_{50} values (expressed in terms of lung burden) were 1,700 μg (confidence limits 1,300-2,100) for inhalation exposure and 2,100 μg (confidence limits 1,900-2,700) for the lavage study. Although those LD_{50} values were not significantly different, histopathological examination revealed differences in the nature and distribution of pathological changes with the 2 different routes. Those exposed by inhalation died as a result of ulcerative laryngitis and laryngeal oedema and showed only minimal pulmonary lesions. Exposure by lavage by-passed the larynx and animals died from pulmonary oedema and acute exudative pneumonia.

4. PULMONARY TOXICITY OF DIOL-INITIATED POLYMERS (EXPOSURE TO AEROSOLS)

4.1 WATER-INITIATED POLYMERS

4.1.1 75:25 Ethylene Oxide, Propylene Oxide Random Copolymers

UCON 75-H-1400 (av. MW 2,200)

Sub-acute inhalation toxicity (Appendix C)

In a study designed to evaluate the effects of inhalation of aerosols of a range of PAG (Warheit *et al*, 1995), a group of male Crl:CDBR rats was exposed (nose only) to an aerosol concentration of 111.7 mg UCON 75-H-1400/m^3, 6 h/d, for three consecutive days. Five sub-groups of 3 or 4 animals were subject to a bronchoalveolar lavage procedure 0, 2 or 7 days, one month or 3 months after the final exposure; the lavage fluid was examined for cell count and viability, differential cell count, biochemistry (enzymes and protein), macrophage cell culture and phagocytosis assay (including SEM). Two further sub-groups of 4 animals were used for pulmonary cell-labelling investigations (5-bromo-2-deoxyuridine labelling followed by perfusion fixation) immediately after the third exposure and 7 days later; the animals killed after 7 days were also used for histopathological evaluation. Control animals were exposed to air only.

All animals survived without apparent ill effects. Evaluation of the bronchoalveolar lavage fluid revealed evidence of only minor, transient pulmonary inflammation. The results of biochemical analysis of the lavage fluid revealed no significant changes related to inhalation exposure. Cell-labelling investigations similarly revealed no effect of exposure to UCON 75-HB-1400. On histopathological evaluation 7 days after the final exposure, the lungs of treated animals appeared normal.

In a separate study, groups of 10 male Sprague-Dawley rats were exposed (whole-body) to an aerosol concentration of 191mg/m^3 UCON 75-H-1400 for 6h/d, for a total of 9 exposures during an 11-day period (Ulrich *et al*, 1992). Five animals from each group were then sacrificed and the remaining animals maintained for 2-week recovery period before being sacrificed. During and after exposure there were essentially no signs of toxicity. Body weights throughout the exposure period were similar to the control group; at the time of sacrifice no changes were detected in organ weights or in the haematological parameters examined. No exposure-related macroscopic changes were noted at post-mortem examination. In most exposed animals there was minimal alveolitis which was considered to be treatment-related and consisted mostly of scattered intra-alveolar macrophages and neutrophils and slightly hypercellular alveolar interstices. Most macrophages had foamy cytoplasm, indicative of

phagocytic activity. No exposure-related differences were noted on body weights, organ weights, macroscopic observations at post mortem or microscopic findings in those animals maintained for the 2-week recovery period. The histopathological LOAEL was determined in a subsequent review of the lung slides of this study. The LOAEL for UCON 75-HB-1400 was ~ 200 mg/m^3 (Lewis, 1995).

UCON 75-H-9500 (av. MW not available)

Acute inhalation toxicity (Appendix A)

Groups of 6 male Crl:CD(SD)BR rats were exposed (nose-only) to aerosol concentrations of 240, 1,200 or 1,700 mg UCON 75-H-9500/m^3 for 4 hours (DuPont, 1985c). During or immediately after exposure, rats in all groups had red nasal discharge; rats at the highest exposure concentration also had red ocular discharge. The ALC for UCON 75-H-9500 exceeded 1,700 mg/m^3.

UCON 75-H-380,000 (av. MW >> 12,000)

Acute inhalation toxicity (Appendix A)

Groups of 6 male Crl:CD(SD)BR rats were exposed (nose-only) to aerosol concentrations of 860, 1,500 or 1,900 mg UCON 75-H-380,000/m^3 for 4 hours (DuPont, 1985d). Dose-dependent weight loss occurred on the first day after exposure only. The ALC for UCON 75-H-380,000 exceeded 1,900 mg/m^3.

4.1.2 Propylene Oxide, Ethylene Oxide Block Copolymers

Pluronic L31 (90:10 Propylene Oxide, Ethylene Oxide; av. MW 1,100)

Acute inhalation toxicity (Appendix A)

Groups of 6 male Crl:CD(SD)BR rats were exposed (nose-only) to aerosol concentrations of 180 or 4,800 mg Pluronic L31/m^3 for 4 hours (DuPont, 1985e). Dose dependent, slight to moderate weight loss occurred on the first day after exposure only. The ALC for Pluronic L31 exceeded 4,800 mg/m^3.

Sub-acute inhalation toxicity (Appendix C)

In a study designed to evaluate the effects of inhalation of aerosols of a range of PAG (Warheit *et al*, 1995), a group of male Crl:CDBR rats was exposed (nose-only) to an aerosol concentration of 109.7 mg Pluronic L31/m^3, 6 h/d, 3 consecutive days. Five sub-groups of 3 or 4 animals were subject to a bronchoalveolar lavage procedure 0, 2 or 7 days, one month or 3 months after the final exposure; the

lavage fluid was examined for cell count and viability, differential cell count, biochemistry (enzymes and protein), macrophage cell culture and phagocytosis assay (including SEM). Two further sub-groups of 4 animals were used for pulmonary cell-labelling investigations (5-bromo-2-deoxyuridine labelling followed by perfusion fixation) immediately after the third exposure and 7 days later; the animals killed after 7 days were also used for histopathological evaluation. Control animals were exposed to air only.

All animals survived without apparent ill effects. Evaluation of the bronchoalveolar lavage fluid revealed evidence of only minor, transient pulmonary inflammation. The results of biochemical analysis of the lavage fluid revealed no significant changes related to inhalation exposure. Cell-labelling investigations revealed some labelling of terminal bronchiolar cells in animals sampled immediately after the final exposure similar to that observed in control animals; the data presented do not indicate any adverse biological change. On histopathological evaluation 7 days after the final exposure, the lungs of treated animals appeared normal.

In a separate study, groups of 10 male Sprague-Dawley rats were exposed (whole-body) to an aerosol concentration of 97 mg/m^3 Pluronic L31 for 6h/d, for a total of 9 exposures over 11 days (Ulrich *et al*, 1992). Five animals from each group were then sacrificed and the remaining animals maintained for a 2-week recovery period before being sacrificed. During and after exposure, there were essentially no signs of toxicity. Body weights throughout the exposure period were similar to the control group; at the time of sacrifice no changes were detected in organ weights or in the haematological parameters examined. No exposure-related macroscopic changes were noted at post-mortem examination. In most exposed animals there was minimal alveolitis which was considered to be treatment-related and consisted mostly of scattered intra-alveolar macrophages, neutrophils and slightly hypercellular alveolar interstices. Most macrophages had foamy cytoplasm, indicative of phagocytic activity. No exposure-related differences were noted on body weights, organ weights, macroscopic observations at post mortem, or microscopic findings in those animals maintained for the 2-week recovery period. The histopathological NOAEL was determined in a subsequent review of the lung slides of this study. The NOAEL for Pluronic L31 was ~ 100 mg/m^3 (Lewis, 1995).

Pluronic L64 (60:40 Propylene Oxide, Ethylene Oxide; av. MW 2,900)

Acute inhalation toxicity (Appendix A)

Groups of 6 male Crl:CD(SD)BR rats were exposed (nose-only) to aerosol concentrations of 40, 280 or 1,500 mg Pluronic L64/m^3 for 4 hours (DuPont, 1985f). Clinical signs were confined to rats exposed to 1,500 mg/m^3 and included noisy respiration; slight initial weight loss was also noted in this exposure group. The ALC for Pluronic L64 exceeded 1,500 mg/m^3.

Sub-acute inhalation toxicity (Appendix C)

In a study designed to evaluate the effects of inhalation of aerosols of a range of PAG (Warheit *et al*, 1995), a group of male Crl:CDBR rats was exposed (nose-only) to an aerosol concentration of 99.3 mg Pluronic L64/m^3, 6 h/d, for 3 consecutive days. Sub-groups of 3 or 4 animals were subject to a bronchoalveolar lavage procedure 0, 2 or 7 days, one month or 3 months after the final exposure; the lavage fluid was examined for cell count and viability, differential cell count, biochemistry (enzymes and protein), macrophage cell culture and phagocytosis assay (including SEM). Further sub-groups of 4 animals were used for pulmonary cell-labelling investigations (5-bromo-2-deoxyuridine labelling followed by perfusion fixation) immediately after the third exposure and 7 days later; the animals killed after 7 days were also used for histopathological evaluation. Control animals were exposed to air only.

All animals survived without apparent ill effects. Evaluation of the bronchoalveolar lavage fluid revealed evidence of only minor, transient pulmonary inflammation. The results of biochemical analysis of the lavage fluid revealed only minor increase in alkaline phosphatase activity 7 days after the final exposure. Cell-labelling investigations revealed some labelling of terminal bronchiolar cells in animals sampled immediately after the final exposure similar to that observed in control animals; the data presented do not indicate any adverse biological change. On histopathological evaluation 7 days after the final exposure the lungs of treated animals appeared normal.

In a separate study, groups of 10 male Sprague-Dawley rats were exposed (whole-body) to an aerosol concentration of 103 mg/m^3 Pluronic L64 for 6h/d, for a total of 9 exposures over 11 days (Ulrich *et al*, 1992). Five animals from each group were then sacrificed and the remaining animals maintained for a 2-week recovery period before being sacrificed. During and after exposure there were essentially no signs of toxicity. Body weights throughout the exposure period were similar to the control group; at the time of sacrifice no changes were detected in organ weights or in the haematological parameters examined. No exposure-related macroscopic changes were noted at post-mortem examination. In most exposed animals there was minimal alveolitis which was considered to be treatment-related and consisted mostly of scattered intra-alveolar macrophages, neutrophils and slightly hypercellular alveolar interstices. Most macrophages had foamy cytoplasm, indicative of phagocytic activity. No exposure-related differences were noted on body weights, organ weights, macroscopic observations at post mortem, or microscopic findings in those animals maintained for the 2-week recovery period. The histopathological LOAEL was determined in a subsequent review of the lung slides of this study. The LOAEL for Pluronic L64 was ~ 100 mg/m^3 (Lewis, 1995).

Pluronic L81 (90:70 Propylene Oxide, Ethylene Oxide; av. MW 2,750)

Acute inhalation toxicity (Appendix A)

Groups of 6 male Crl:CD(SD)BR rats were exposed (nose-only) to aerosol concentrations of 710, 1,500, 2,400 or 2,800 mg Pluronic L81/m^3 for 4 hours (DuPont, 1986b). A variety of exposure-related clinical signs was noted in all treated groups. Exposure concentration-related weight loss was recorded, with deaths confined to the two highest exposure groups and occurring within one day of exposure. The ALC for Pluronic L81 was 2,400 mg/m^3 (acute LC_{50} value approximately 2,000 mg/m^3).

Pluronic P84 (60:40 Propylene Oxide, Ethylene Oxide; av. MW 4,200)

Acute inhalation toxicity (Appendix A)

Groups of 6 rats were exposed to aerosol concentrations of 1,500, 2,400 or 2,800 mg Pluronic P84 for 4 hours (Kennedy *et al*, 1990). Four rats exposed at 2,400 mg/m^3 died, as did all rats exposed at 2,800 mg/m^3. Body-weight loss was recorded in those surviving exposure at 2,400 mg/m^3. Amongst animals that died, respiratory difficulty and body-weight losses were recorded before death (acute LC_{50} value approximately 2,000 mg/m^3).

Pluronic L122 (80:20 Propylene Oxide, Ethylene Oxide; av. MW 5,000)

Sub-acute inhalation toxicity (Appendix C)

Groups of 5 male and 5 female Sprague-Dawley rats were exposed (whole-body) to aerosol concentrations of 0, 24, 47 or 67 mg Pluronic L122/m^3, 6 h/d, for 10 days over a 14-day period (Bio/dynamics Inc., 1985). During the exposure period, no treatment-related changes were observed in general condition, ophthalmoscopic examination or body weights. At post-mortem examination on the day after the final (10th) exposure, no treatment-related changes were recorded in any of the groups exposed to Pluronic L122 (either sex). No histopathological examination of the tissues was undertaken.

ICI Block Copolymer A (70:30 Propylene Oxide, Ethylene Oxide; av. MW 4,000)

Sub-acute inhalation toxicity (Appendix C)

Groups of 5 or 10 male and female Sprague-Dawley rats were exposed (whole-body), to aerosol concentrations of 0, 5.0, 50 or 400 mg ICI Block Copolymer A/m^3 for 6 h/d for 10 days over a 14-day period (AlliedSignal, 1993). Five male and 5 female animals from each exposure group were sacrificed at the end of the exposure period and the remaining animals (5 males and 5 females from the control and

the 400 mg/m^3 groups) maintained for a 2-week recovery period before sacrifice. During the exposure period, treatment-related signs were confined to nasal discharge and rales; one female animal exposed to 400 mg/m^3 showed decreased body-weight gain during the exposure period, with a slight recovery thereafter.

At the end of the exposure period, all treated animals showed significant increases in lung weight and this was associated with microscopic evidence of interstitial inflammation and macrophage infiltration in the lungs of all animals. The severity of these changes was dose-related. Other findings, confined to the 50-400 mg/m^3 groups, included the development of lung abscesses (2 males and 1 female exposed to 400 mg/m^3), hypertrophy/hyperplasia of the bronchiolar epithelium in 5 males and 4 females exposed to 400 mg/m^3 and, to a lesser extent in 2 males exposed to 50 mg/m^3. The severity and/or incidence of these findings in the post-exposure recovery animals was only slightly less than observed at the end of the exposure period, indicating that no substantial recovery had occurred. At the end of the exposure period no NOEL could be determined. The histopathological NOAEL and LOAEL were determined in a subsequent review of the lung slides of this study. The NOAEL for ICI Block Copolymer A was < 5 mg/m^3 and the LOAEL ~ 5 mg/m^3 (Lewis, 1995).

ICI Block Copolymer B (80:20 Propylene Oxide, Ethylene Oxide; av. mol. wt 12,000)

Sub-acute inhalation toxicity (Appendix C)

Groups or 5 and 10 male and female Sprague-Dawley rats were exposed (whole-body), to aerosol concentrations of 0, 6.1, 52 or 300 mg ICI Block Copolymer B/m^3 for 6 h/d for 10 days over a 14-day period (AlliedSignal, 1993). Five male and 5 female animals from each exposure group were sacrificed at the end of the exposure period and the remaining animals (5 males and 5 females from the control and the 300 mg/m groups) maintained for 2- week recovery period before sacrifice.

At the end of the exposure period, animals exposed to 300 mg/m^3 showed significant increases in lung weight and this was associated with microscopic evidence of interstitial inflammation and macrophage infiltration. The microscopic pathology findings were seen to a lesser degree in the animals exposed to 52 mg/m^3. At the end of the post-exposure recovery period the severity of the findings in the animals exposed to 300 mg/m^3 was similar to those seen at the end of the exposure period, indicating that no significant recovery had occurred. The histopathological NOAEL and LOAEL were determined in a subsequent review of the lung slides of this study. The NOAEL for ICI Block Copolymer B was ~ 5 mg/m^3 and the LOAEL ~ 50 mg/m^3 (Lewis, 1995).

4.1.3 Ethylene Oxide, Propylene Oxide Reverse Block Copolymers

Pluronic 17R1 (10:90 Ethylene Oxide, Propylene Oxide; av. MW 1,900)

Sub-acute inhalation toxicity (Appendix C)

Groups of 10 male Sprague-Dawley rats were exposed (whole-body) to an aerosol concentration of 102 mg Pluronic 17R1/m^3 for 6h/d, for a total of 9 exposures over 11 days (Ulrich *et al*, 1992). Five animals from each group were sacrificed and the remaining animals maintained 2-week recovery period before being sacrificed. During and after exposure there were essentially no signs of toxicity. Body weights throughout the exposure period were similar to the control group; at the time of sacrifice no changes were detected in organ weights or in the haematological parameters examined. There were no exposure-related macroscopic changes noted at post mortem. In most exposed animals there was minimal alveolitis which was considered to be treatment-related and consisted mostly of scattered intra-alveolar macrophages, neutrophils and slightly hypercellular alveolar interstices. Most macrophages had foamy cytoplasm, indicative of phagocytic activity. No exposure-related differences were noted on body weights, organ weights, macroscopic observations at post mortem, or on microscopic findings in those animals maintained for the 2-week recovery period. The histopathological NOAEL was determined in a subsequent review of the lung slides of this study. The NOAEL for Pluronic 17R1 was ~ 100 mg/m^3 (Lewis, 1995).

Pluronic 31R1 (15:85 Ethylene Oxide, Propylene Oxide; av. MW 3,700)

Sub-acute inhalation toxicity (Appendix C)

Groups of 5 or 10 male and female Sprague-Dawley rats were exposed (whole body), to aerosol concentrations of 0, 5.4, 50 or 430 mg Pluronic 31R1/m^3 for 6 h/d for 10 days out of a 14 day period (AlliedSignal, 1993). Five male and 5 female animals from each exposure group were sacrificed at the end of the exposure period and the remaining animals (5 males and 5 females from the control and the 430 mg/m^3 groups), maintained for a 2-week recovery period before sacrifice. During the exposure period, treatment-related signs were confined to nasal discharge and rales. Rats exposed to 430 mg/m^3 showed decreased body-weight gain and food consumption during the exposure period, with recovery thereafter.

At the end of the exposure period animals exposed to 430 mg/m^3 showed significant increases in lung weight and this was associated with microscopic evidence of generally dose-related interstitial inflammation and macrophage infiltration in the lungs of all treated animals. Other findings confined to the 430 mg/m^3 group included hypertrophy/hyperplasia of the bronchiolar epithelium in 5 males and 2

females. The severity and/or incidence of these findings in the post-exposure recovery animals was less than that observed at the end of the exposure period. This indicated that although some recovery had occurred, the process was not complete (AlliedSignal, 1993). The histopathological NOAEL and LOAEL were determined in a subsequent review of the lung slides of this study. The NOAEL for Pluronic 31R1 was ~ 50 mg/m^3 and the LOAEL ~ 430 mg/m^3 (Lewis, 1995).

4.1.4 100% Ethylene Oxide Polymers

Polyethylene Glycol (PEG) 200 (av. MW 200)

Acute inhalation toxicity (Appendices A and B)

Groups of 6 male and 6 female Fischer 344 rats and B6C3F$_1$ mice were exposed (whole-body) to an aerosol concentration of 2,516 mg PEG 200/m^3 for 6 hours (Crook *et al*, 1980a). All animals survived and no toxic signs were noted during exposure and the 14-day post-exposure period. No significant abnormalities were detected in the blood chemistry or haematological parameters examined at the end of the observation period. Respiratory physiology measurements on days 1 and 14 post-exposure also failed to detect any significant difference between control and treated animals. No treatment-related effects were seen on histopathological examination of the tissues.

Sub-chronic inhalation toxicity (Appendix D)

Groups of 15 male and 15 female Fischer 344 rats and B6C3F$_1$ mice were exposed (whole-body) to aerosol concentrations of 122 or 1,001 mg PEG 200/m^3 6 h/d, 5 d/wk for up to 13 weeks (Crook *et al*, 1980b). Five male and 5 female rats and mice per treatment group were sacrificed after 6 weeks and 13 weeks; the remaining animals were maintained without further treatment for a 3-day recovery period. No toxic signs were observed during or after exposure. There were no treatment-related deaths. Haematological blood chemical, respiratory physiological and histopathological examination failed to reveal any exposure-related effect after 6 or 13 weeks of treatment or at the end of the 3-day recovery period.

Polyethylene Glycol (PEG) 3350 (Av. MW 3,350)

Sub-acute inhalation toxicity (Appendix C)

Groups of 10 or 20 Fischer rats per sex were exposed (whole-body) for 6 h/d, for a total of 9 exposures over 11 days to aerosol concentrations of 0, 109, 567 or 1,008 mg PEG 3350/m^3 PEG 3350 (Klonne *et al*, 1989b). Ten control animals per sex and 10 animals per sex exposed to the highest concentration were maintained for a 2-week recovery period. The principal exposure-related effects were decreased body-

weight gain in male animals exposed to 567 or 1,008 mg/m^3 and an increased total neutrophil count in male animals exposed to 1,008 mg/m^3. Absolute lung weights of both sexes were increased in the 567 and 1,008 mg/m^3 groups. The magnitude of the lung-weight increase was lower after 2-week recovery period, but lungs remained heavier than those of the control group. No exposure-related lesions were observed at post-mortem examination. Exposure-related histopathological lesions were observed only in the lung and occurred in a concentration-related manner in all PEG 3350-related groups at the end of the exposure phase. The lesions were generally minimal-to-mild in severity and confined to an increase in intra-alveolar macrophages; these had a foamy vacuolated cytoplasm. At the end of the recovery period there was still a minimal/mild increase in the number of macrophages in the lungs of rats treated with 1,008 mg/m^3. There was no indication of cellular necrosis or of necrotic debris in the lung. This histological finding was considered to reflect a mild, generalised response of the lung to inhaled particulate.

4.2 PROPYLENE GLYCOL-INITIATED POLYMERS

4.2.1 100% Propylene Oxide Polymers

The inhalation of mists of low MW (200-1,200) polypropylene glycols, particularly when heated, are considered to be potentially hazardous although the higher MW ($\geq$ 2,000) are of low toxicity (Rowe and Wolf, 1982).

5. PULMONARY TOXICITY OF TRIOL-INITIATED POLYMERS (EXPOSURE TO AEROSOLS)

5.1 GLYCEROL-INITIATED POLYMERS

5.1.1 50:50 Ethylene Oxide, Propylene Oxide Random Copolymers

Polyglycol 15-200 (av. MW 2,600)

Acute inhalation toxicity (Appendix A)

Groups of 6 male Fischer 344 rats were exposed (whole-body) to aerosols of Polyglycol 15-200 for 4 hours at concentrations of 1,000 mg/m^3 or 1,200 mg/m^3 (the highest attainable concentration) (Dow Chemical, 1985). No treatment related effects were observed during the exposure phase or the 14-day post-exposure observation period. There was no mortality during the study; the rate of body-weight gain and final body weights of test animals were within the normal range for untreated rats of this strain and age. No pathological examination was carried out, but on the basis of data available, it was concluded that Polyglycol 15-200 did not pose any significant acute inhalation hazard.

6. INVESTIGATION OF THE MECHANISM OF PULMONARY TOXICITY EXHIBITED BY SELECTED ETHYLENE OXIDE, PROPYLENE OXIDE RANDOM COPOLYMERS

6.1 *IN VITRO* STUDIES

The *in vitro* cytotoxic potential of selected EO-PO copolymers was assessed in 3 different preparations of isolated cells: a rat epithelial cell line (LEC), a rat primary alveolar macrophage isolate (RAM) and a Chinese Hamster ovary-derived cell line (AS52) (Monsanto, 1991). Copolymers were incubated with the cell preparations for 24 hours at concentrations of 10-20,000 µg/ml. Lactate dehydrogenase (LDH) leakage into the medium was measured and expressed as % of LDH released by a cell preparation totally lysed with 0.1% TRITON X-100. The concentration estimated to give 50% LDH release was calculated for each of the copolymers.

Table 3: Effect of PAG on Rat Cells in Culture

Copolymer	EC_{50} (µg/ml)*		
	LEC	RAM	AS52
Pluronic 17R1	300	200	400
Pluronic L31	4,000	3,000	4,000
Pluronic L64	400	400	400
UCON 50-HB-260	11,000	4,000	>20,000
UCON 50-HB-660	>20,000	4,000	>20,000
UCON 50-HB-2000	>20,000	>20,000	>20,000
UCON 50-HB-5100	>20,000	>20,000	>20,000
UCON 75-H-1400	>20,000	>20,000	>20,000

* For LDH leakage

Each of the materials tested gave a similar rank order of cytotoxicity in the 3 cell types. This rank order did not, however, correspond to the inhalation toxicity of these materials.

6.2 *IN VIVO* STUDIES

6.2.1 Studies by Routes other than Inhalation

Intratracheal installation

Seven materials from the UCON 50-HB and UCON LB product range (Table 4) were administered to rats by intratracheal instillation (Union Carbide, 1989b); control rats were treated with saline. The animals were allowed to recover from the anaesthetic and kept for up to 14 days before sacrifice.

With UCON LB PAG, Tergitol 24-L-60N and low MW UCON HB PAG, deaths typically occurred a few minutes after instillation. Instillation of the higher MW materials, 50-HB-2000 and 50-HB-5100, resulted in delayed deaths preceded by body-weight loss or reduced weight-gain, increased lung weight, and histopathological changes in the lungs including haemorrhage, perivascular infiltrates and interstitial pneumonitis (Table 4).

Table 4: Effects of PAG in Rats by Intratracheal Instillation

Test Material	Dosage (mg/kg)	Outcome
UCON 50-HB-260	0.05	Mortality (rapid)
	0.02	No mortality
UCON 50-HB-2000	0.05	Mortality (some delayed)
	0.02	5/15 died after 3-5 days
UCON 50-HB-5100	0.05	Mortality (some delayed)
	0.02	7/15 died after 3-5 days
UCON 50-HB-660	0.2	Mortality (generally rapid)
	0.1	No mortality
UCON LB-65*	0.01	Mortality (rapid)
	0.05	No mortality
UCON LB-1145*	2.0	No mortality
UCON LB-3000*	2.0	Mortality (rapid)
	1.0	No mortality
TERGITOL 24-L-60N**	0.01	Mortality (rapid)
	0.005	No mortality
Saline	2.0	No mortality

* UCON LB lubricants are homopolymers of propylene oxide, initiated on butanol
** TERGITOL 24-L-60N is an ethoxylated C_{12}-C_{14} linear alcohol

Intravenous Administration

The acute toxicities of 7 materials from the UCON 50-HB and 50-H lubricant series were determined following intravenous injection (Union Carbide, 1990a). The materials listed in Table 5, used as supplied

or diluted in normal physiological solution, were injected into the tail vein of groups of 5 male and 5 female rats of the Sprague-Dawley strain; effects were assessed for 14 days after dosing.

The results revealed that the most acutely toxic copolymers were those with lower MW. Similar signs of toxicity, i.e. laboured breathing, tremor, convulsions, discharge, foam around the mouth and prostration, were reported for all grades. Death generally occurred within minutes, especially with lower MW materials. However, death up to 6 days after dosing occurred with the higher MW copolymers.

Table 5: Effects of PAG in Rats by Intravenous Injection

UCON Copolymer	Intravenous LD_{50} values (mg/kg)		Time to Death
	Male	Female	
50-HB-260	0.20 (0.14-0.34)†	0.21 (0.14-0.32)†	< 5 minutes
50-HB-660	0.41 (0.30-0.56)	0.64 (0.54-0.75)	< 15 minutes
50-HB-2000	1.62 (1.18-2.24)	2.00 (1.18-3.39)	≤ 4 days
50-HB-5100	2.14 (1.45-3.17)	2.00 (1.18-3.39)	≤ 5 days
50-HB-5100R*	2.14 (1.45-3.17)	1.66 (1.42-1.93)	≤ 4 days
75-H-1400	3.25 (2.02-5.24)	6.73 (2.69-16.8)	≤ 5 days
50-H-5100**	4.29 (2.90-6.34)	4.29 (2.90-6.34)	≤ 6 days

* Reduced copolymer, see Section 6.2.2
** Special preparation, see Section 6.2.2
† 95% confidence limits

Gross pathological change was usually limited to discoloration of the lungs, livers, kidneys and thymus. Histopathological changes in the lungs were most apparent in rats receiving the UCON 50-HB-5100. UCON 50-H-5100 and 75-H-1400 produced less-severe microscopic lung injury, whilst UCON 50-HB-260 and 50-HB-2000 caused minimal changes and no treatment-related lesions were apparent among rats dosed with UCON 50-HB-660. In animals treated with the UCON 50-HB-5100, inflammation, alveolar histiocytosis and fibrosis were recorded.

Thus, only the higher MW UCON 50-HB copolymers produced the type of lung injury seen on inhalation exposure; the lung pathology and several of the clinical signs suggested that the lung is a major target organ for this series of chemicals when administered by the intravenous route.

A further study (Union Carbide, 1992) was conducted in an attempt to elucidate the pathogenesis of lung lesions produced by UCON 50-HB-5100. Groups of rats received the material by intravenous injection at a single dose of 1.75 ml/kg (as a 60% dilution in physiological saline, at a dose of 2.92 mg/kg). Animals

were sacrificed at various times up to 14 days after injection. Effects on the lungs was evaluated by bronchoalveolar lavage (BAL) and light and electron microscopy.

BAL indicated an influx of WBCs, RBCs, proteins and enzymes, beginning on day 1 and peaking by days 3-4; the response had mostly subsided by day 14. The morphologic evaluations correlated well with BAL findings, with interstitial pneumonitis increasing in severity by days 3 and 4 leading to interstitial fibrosis by day 14. The ultrastructural findings indicated that the earliest and most-severe damage was to the alveolar epithelial cells as shown by oedema of the cytoplasm, alterations in the organelles and fragmentation of membranes. Similar and less-severe changes in endothelial cells were also seen; this damage was most severe by day 3. By day 7 most of the inflammatory and degenerative changes had subsided and there was proliferation of Type II pneumocytes. The light microscopic changes were the same as those seen following inhalation exposure to an aerosol of this copolymer. The study confirms that the lungs are similarly damaged following exposure by either route and that the lung is a specific target organ. The target cell is most likely the Type I pneumocytes lining the alveoli.

6.2.2 Inhalation Studies with Specially-prepared Copolymers

UCON 50-HB-5100R (av. MW wt. 4,000)

The acute inhalation toxicity of a modified sample of UCON 50-HB-5100 was determined (Appendix A); the sample was prepared from a commercial sample of UCON 50-HB-5100 (Table 2) by hydrogenation over Raney Nickel, with the intention of reducing the degree of unsaturation, particularly the presence of allyl groups (Union Carbide, 1990b).

Groups of 5 male and 5 female Sprague-Dawley rats were exposed to aerosol concentrations of 80, 120, 370 or 740 mg UCON 50-HB-5100R/m^3 for 4 hours. Blepharospasm during exposure, the only clinical sign related to treatment, was seen on exposure to 370 or 740 mg/m^3. Deaths occurred after 3-8 days; all animals died when exposed to 740 and 370 mg/m^3, 5/10 died at 120 mg/m^3 and 0/10 at 80 mg/m^3. Loss of body weight or reduced weight-gain were noted at the 2 lowest exposure concentrations. Post-mortem examination of the animals that died revealed discoloration of the lungs, enlarged sub-mandibular lymph nodes, corneal opacity, periocular encrustation and yellow mucous in the stomach. Amongst animals killed 14 days after exposure to 120 mg/m^3, incomplete collapse of the lungs, occasionally with red discoloration, was recorded. The acute inhalation LC_{50} Of UCON 50-HB-5100R was calculated to be 150 mg/m^3 (95% confidence limits 100-230 mg/m^3).

UCON 50-H-5100 (av. MW 4,000)

The acute inhalation toxicity of water-initiated 50:50 EO-PO random copolymer was determined in groups of 5 male and 5 female Sprague-Dawley rats (Union Carbide, 1990c). This grade of copolymer is not

commercially available, having been prepared specifically for this investigation. Animals were exposed to UCON 50-H-5100 at aerosol concentrations of 200, 460 or 820 mg/m^3 for 4 hours (Appendix A).

Clinical signs related to treatment were seen only at the highest exposure concentration (820 mg/m^3); perinasal wetness and encrustation occurred during exposure; an isolated case of periocular encrustation was seen during the observation period. Deaths occurred after 3-7 days; all rats died at 820 mg/m^3, 8/10 at 460 mg/m^3 and 1/10 at 200 mg/m^3. Loss of body weight or reduced weight-gain were recorded at both the intermediate and lower exposure concentrations. Post-mortem examination of the animals that died revealed discoloured lungs, liver and kidneys. The remainder of the animals had no treatment-related macroscopic changes when killed 14 days after exposure.

The acute inhalation LC_{50} value was calculated to be 340 mg/m^3, with 95% confidence limits of 230 to 520 mg/m^3.

7. DISCUSSION OF ANIMAL STUDY DATA

The absence of reports of significant adverse health effects in humans during the widespread use of PAG for more than five decades supports the view that these materials are safe in industrial use. The materials range in physical form from mobile liquids to waxy solids and all exhibit low volatility which ensures that exposure to their vapours at ambient temperature is low. In common with many other organic compounds, heating the materials at high temperatures leads to oxidative degradation and production of more highly acutely-toxic compounds including ketones, aldehydes and acids (Donbrow, 1987); uses which produce such degradation are avoided. The lubricant properties and water solubility of PAG have been exploited in their use as cutting fluids and fibre lubricants. In both applications aerosols can be generated at ambient temperatures, so the screening of these materials for inhalation toxicity of their aerosols was prudent. In view of their past record of safety, the results of the inhalation investigations on a narrow sub-class of PAG were unexpected. The information reviewed in this report is summarised at the end of this section in Table 7.

Whole-body or nose-only aerosol inhalation studies in rats, have consistently shown that certain butanol-initiated random 50:50 EO-PO copolymers are toxic to the lungs. In 4-hour exposure studies, the LC_{50} values of such copolymers of MW $\leq$ 1,700 was of the order of 4,000-5,000 mg/m^3, while those of MW 2,900 had an LC_{50} of approximately 350 mg/m^3, and those of MW $\geq$ 4,000 were in the range 75-150 mg/m^3. Deaths were not immediate but delayed for up to 8 days after exposure and were associated with characteristic damage to the lungs. Rats were somewhat more sensitive than other species to the toxic effects of the copolymer, but a similar pattern of acute inhalation toxicity was seen in a variety of animal species exposed to aerosols of 4,000 MW copolymer. All rodent species tested showed similar and consistent damage to the lungs and there was also evidence of adverse effects of these materials on the lungs of dogs.

On the other hand, acute aerosol inhalation toxicity data on diol- and triol-initiated PAG, and copolymers with different proportions of EO and PO demonstrate that this pattern of lung toxicity is not a feature of all PAG.

Studies of the effects of repeated exposure to aerosols of the affected copolymers have confirmed that the lung is the primary site of toxic action. The NOAEL of a 50:50 EO-PO random (MW 970) was ~ 500 mg/m^3 in a 2-week rat inhalation study; whilst for copolymers of similar composition (MW 4,000) evidence of damage to the lungs was seen following exposure to a concentration of only 0.9 mg/m^3. In the only 90-day aerosol inhalation study in rats on material of this type, significant effects on the lungs were seen at 0.3 mg/m^3 and no no-effect-concentration was established. Haemorrhage, interstitial pneumonia, Type II pneumocyte hyperplasia and focal or multifocal fibrosis were all still present in the lungs of rats repeatedly exposed to a butanol-initiated 50:50 EO-PO random copolymer (MW 4,000) at the end of a 5-week

recovery period. A similar spectrum of lesions could be anticipated following repeated exposures to other affected copolymers.

Whole-body sub-acute inhalation exposures to some block copolymers (10 exposures over 14 days) have also demonstrated lung toxicity. A block copolymer (ICI A; MW 4,000) induced bronchiolar hyperplasia in the rat lung at 400 mg/m^3 with inflammatory changes observed after exposure to concentrations as low as 5 mg/m^3. Less-severe effects were detected after inhalation exposure to a higher MW copolymer (ICI B; 12,000). These effects were confined to inflammatory changes at 300 and 53 mg/m^3; no effects were observed at 6.1 mg/m^3. A reverse block copolymer (MW 3,700), when tested under identical conditions, induced changes at 430 mg/m^3; the NOAEL was estimated to be 50 mg/m^3.

The recent study by Warheit *et al* (1995) examined the effects on the rat lung of 3 exposures on subsequent days to a range of copolymers; the nature of the changes in the lung recorded and the severity of the findings for the different types of copolymer were consistent with the results of the previous sub-acute studies employing 9 daily exposures.

A comparative review of the rat lung pathology of a sub-set of the random and block-copolymer sub-acute inhalation exposure studies was undertaken to establish a basis for comparison of the study findings published by different groups of investigators (Lewis, 1995). This review included UCON 50-HB-260, UCON 50-HB-660, UCON 50-HB-5100, and UCON 75-H-1400 and the block copolymers Pluronic L31, Pluronic L64, Pluronic 17R1, Pluronic 31R1 and ICI block copolymers A and B (MW 4,000 and 12.000 respectively). The review demonstrated that all copolymers examined, with one exception (UCON 50-HB-260), produced the same lesion in the rat lung, but to a different degree. The changes in the lung ranged from a histiocytosis characterised by an increase in alveoli macrophages (accompanied by macrophage enlargement and vacuolation) to a bronchiolitis (characterised by more pronounced inflammation, accumulation of cellular debris in the airways, degeneration and regenerative epithelial damage). The severity of effects is summarised in Table 6, which includes a corresponding NOAEL and LOAEL for each copolymer. These values may differ from those reported by the authors of the original studies.

Table 6: Comparative Review of the Lung Pathology Slides from a Sub-set of the Sub-acute Inhalation Studies in Rats (Lewis, 1995)

Copolymer	MW	Copolymer type*	NOAEL	LOAEL (and effects)
UCON 50-HB-5100	4,000	Butanol 50/50 random	< 5 mg/m^3	~ 5 mg/m^3 (grade 1 alveolitis)
ICI Block Copolymer A	4,000	Block A 70/30	< 5 mg/m^3	~ 5 mg/m^3 (grade 1 histiocytosis)
ICI Block Copolymer B	12,000	Block B 80/20	~ 5 mg/m^3	~ 50 mg/m^3 (grade 1 histiocytosis)
Pluronic 31R1	3,700	Reverse block 15/85	~ 50 mg/m^3	430 mg/m^3 (bronchiolitis)
Pluronic L31	1,100	Block 90/10	~ 100 mg/m^3	-
Pluronic 17R1	1,900	Reverse block 90/10	~ 100 mg/m^3	-
Pluronic L64	2,900	Block 60/40	-	~ 100 mg/m^3 (grade 1 alveolitis)
UCON 75-H-1400	2,200	Random 25/75	-	~ 200 mg/m^3 (grade 1 histiocytosis)
UCON 50-HB-660	1,700	Random 50/50	-	~ 500 mg/m^3 (grade 2 alveolitis)
UCON 50-HB-260	970	Random 50/50	~ 500 mg/m^3	-

* See also Table 2, Section 2.4

PAG exhibit a spectrum of surfactant activity, which has been suggested to be the basis for the toxic effects observed. However, there is little variation in surfactancy within the group of 50:50 EO-PO random copolymers which, on the other hand, demonstrate a wide range of lung toxicity. With highly surface active TRITON X-100, the pattern of toxic effects in the lung was different from that seen with the 50:50 random copolymers. Furthermore, inhalation of TRITON X-100 aerosols resulted in pathological changes that were different from those seen following exposure by a bronchopulmonary lavage technique (the pattern of changes was dependant on the route of exposure); exposure to TRITON X-100 did not result in delayed deaths in either case.

Thermal degradation of PAG will lead to the formation of ketones, aldehydes and acids which could result in irritation and damage to the lungs and mucous membranes. However such conditions were avoided in generating the aerosols in the studies reported in this review.

Although a large number of by-products may be present in PAG, the fact that similar random and block copolymers produced by several manufacturers have demonstrated the same effect, albeit with different potency, would suggest that activity is related to a major, rather than a trace, component. Components which increase in proportion once the average MW of the copolymer exceeds 2,000 are most likely to be responsible. Investigations of the higher MW 50:50 random copolymers prompted the suggestion that the increased degree of unsaturation in the molecule might be responsible for the effects in the lung. A sample of 4,000 MW copolymer was treated to remove the unsaturation (UCON 50-HB-5100 R). Although the toxicity of this copolymer was not found to be markedly different from that of the parent, no

analysis was conducted to determine if hydrogenation of the double bonds had been successful; the significance of this result, therefore, is equivocal with respect to elucidating the toxic component.

The acute toxicity of a specially-prepared sample of water-initiated UCON 50-H-5100 copolymer demonstrated that lung toxicity might depend, at least in part, on the nature of the initiator used; the data indicated that the acute toxicity of this copolymer was significantly less than that of the equivalent butanol-initiated copolymer of similar MW and EO-PO composition. Thus, taken together, the available data suggest that MW, EO-PO ratio and polymer initiator may all be important determinants of the lung toxicity of these products.

Studies on a range of butanol-initiated copolymers by the intravenous and intratracheal routes of exposure revealed that the acute lethality decreased with increasing MW; this pattern is typical of the toxic response to most polymers. However, with these particular PAG, super-imposed on this was an increasing incidence of delayed deaths with increasing MW. The lung pathology occurring after intravenous injection of random copolymers (especially at 3,700 MW) was typical of that seen in aerosol inhalation studies, and shows the lung to be a specific target tissue for these materials. The studies suggest that after injection, the higher MW polymers are transported via the blood and are taken up by a specific cell in the lung. The absence of corresponding toxicity following oral or dermal exposure is likely, as such polymers are poorly absorbed by these routes and may be metabolised at a rate sufficient to keep blood levels below the threshold for pulmonary toxicity. Absorption studies using ^{14}C-labelled UCON 50-HB-260 and UCON 50-HB-5100 have confirmed that although the lower MW copolymer is both absorbed and metabolised following ingestion, the higher MW material is poorly absorbed (Rowe and Wolf, 1982).

Investigation of the effects of PAG on various types of cell grown in culture failed to confirm any particular sensitivity to copolymers which cause lung toxicity. It is widely acknowledged that the morphology, uptake mechanisms and metabolic capacity of lung epithelial cells grown in culture are rapidly impaired. Lung epithelial cells rapidly lose biochemical and morphological phenotype and this de-differentiation starts within 12 hours of isolation. The findings thus do not assist in the elucidation of a mechanism of toxicity to such cells *in vivo*.

Lung lavage studies, conducted after intravenous or inhalation exposure to high MW polymer, have confirmed that a similar pattern of pathological changes occurs by both routes of exposure. The pattern of changes suggests that unmetabolised, higher MW 50:50 random copolymer in the blood may be taken up by lung epithelial cells (perhaps by a fatty acid transport mechanism); ultrastructural studies indicate that the earliest and most severe damage was to the alveolar epithelial cells, particularly the Type I pneumocyte lining the alveoli.

In the future, screening of selected alkoxylates for adverse effects on the lung using intravenous injection (for example in mice) and histopathology of the lungs to detect injury, would offer an opportunity to

examine a wide range of chemicals when only small quantities are available; special copolymers or samples of 'impurities' may be difficult and expensive to produce.

Table 7: Summary of Rat Acute, Sub-acute and Sub-chronic Toxicity Data on PAG

Initiator	Name	Average MW	EO-PO ratio	Type	Acute Tox. LC_{50} (mg/m^3)	Original NOAEL[1] (mg/m^3)	Path. WG NOAEL[2] (mg/m^3)
MONOLS							
Butanol	UCON* 50-HB-170	730	50:50	Random	> 5,100	-	-
	UCON* 50-HB-260	970	50:50	Random	~ 5,000	500	~ 500
	UCON* 50-HB-660	1,700	50:50	Random	~ 4,500	500	< 500
	UCON* 50-HB-2000	2,900	50:50	Random	~ 350	< 50	-
	UCON* 50-HB-5100	4,000	50:50	Random	~ 100	< 5	< 5
	UCON* 50-HB-5100R**	4,000	50:50	Random	~ 150	-	-
	ICI Copolymer	4,000	50:50	Random	~ 75[3]	-	-
	Pluracol* W-5100	4,200	50:50	Random	~ 150	-	-
	ICI Copolymer	4,500	50:50	Random	~ 75[3]	-	-
Octylphenol	TRITON* X-100 †	647	100% EO	Homopolymer	~ 1,800	-	-
DIOLS							
Water (or	UCON* 50-H-5100	4,000	50:50	Random	~ 350	-	-
diethylene	UCON* 75-H-1400**	2,200	75:25	Random	-	< 200	< 200
glycol, or	UCON* 75-H-9500	Not known	75:25	Random	> 1,700	-	-
dipropylene	UCON* 75-H-380,000	>> 12,000	75:25	Random	> 1,900	-	-
glycol)	Pluronic* L31	1,100	10:90	Block	> 4,800	100	~ 100
	Pluronic* L64	2,900	40:60	Block	> 1,500	< 100	< 100
	Pluronic* L81	2,750	10:90	Block	~ 2,000	-	-
	ICI Block copolymer A	4,000	30:70	Block	-	< 5	< 5
	Pluronic* P84	4,200	40:60	Block	~ 2,000		
	Pluronic* L122	5,000	20:80	Block	-	-	-
	ICI Block copolymer B	12,000	80:20	Block	-	5	~ 5
	Pluronic* 17R1	1,900	10:90	Reverse Block	-	100	~ 100
	Pluronic* 31R1	3,700	15:85	Reverse Block	-	50	~ 50
	Polyethylene glycol 200	200	100% EO	Homopolymer	> 2,500	-	-
	Polyethylene glycol 3350	3,350	100% EO	Homopolymer	-	<100	-
TRIOLS							
Glycerol	Polyglycol 15 - 200	2,600	50:50	Random	> 1,200	-	-

[1] As described in the original study report/publication
[2] As re-evaluated from the original slides by a Pathology Working Group
[3] Lethality after 2 and 6 hour single exposure
* Trade name
** Not commercially available
† Hamster study

8. EFFECTS ON MAN

8.1 WORKPLACE MONITORING

An industrial hygiene study was conducted to develop a sampling method, validate analytical procedures and obtain an estimate of workplace concentrations of a PAG aerosol. Workplace concentrations of a lubricant formulation containing UCON 50-HB-660 were generally less than 0.4 mg/m^3 (Union Carbide, 1984). Details of the workplace and formulation are not available.

8.2 HEALTH EFFECTS

There are no reports of adverse effects arising from exposure to vapours produced at ambient temperature or to aerosols of any of the copolymers discussed in this report.

9. GENERAL CONCLUSIONS

- PAG generally present a low toxic hazard and have been used safely for many years. Nevertheless, aerosol inhalation studies in experimental animals have revealed the lung as a target organ for some specific types of copolymers. This finding has been confirmed in several laboratories using copolymers manufactured by different companies.

- Pulmonary toxicity has been demonstrated in acute inhalation studies with random EO-PO 50:50 copolymers of MW 2,900-4,500 (the highest MW tested). These effects have been seen in several laboratory animal species.

- In longer-term (sub-acute) inhalation studies similar lung effects have been seen with the same random copolymers and, in addition, in certain types of block and reverse block copolymers of similar and higher MW.

- Pathological changes in the lung observed by light microscopy were congestion, haemorrhage, interstitial pneumonia and Type II pneumocyte hyperplasia with interstitial focal fibrosis after longer periods of exposure. Electron microscopy has suggested that the Type I pneumocyte lining the alveoli is a primary target cell.

- It is recognised that higher MW copolymers are inherently more likely to contain 'impurities'; limited testing has thus far failed to confirm the role of these 'impurities' as contributing to the observed pulmonary toxicity.

- Thermal degradation can lead to the formation of a range of noxious materials, including ketones, aldehydes and acids.

- The same, specific pattern of lung damage is evoked by the same types of copolymers when given to rats via the intravenous or intratracheal routes.

- No evidence of significant lung toxicity was seen following exposure to aerosols of butanol-initiated random 50:50 EO-PO copolymers having MW lower than 2,900, or having different EO-PO ratios (irrespective of MW) or with copolymers initiated on glycerol.

- Workplace exposure to aerosols of the more toxic copolymers (or to formulated products containing them) should be adequately controlled in view of their potential to cause permanent damage to the lung.

APPENDIX A: SUMMARY OF 4-HOUR ACUTE INHALATION TOXICITY STUDIES IN RATS

Product (av. MW)	Atmosphere Concentration (mg/m^3)*	Aerosol Details MMAD[a] (μm)	Aerosol Details GSD[b]	Mortality	Findings	Reference
Butanol-initiated 50:50 Random Copolymers						
UCON 50-HB-170	410 [cl]	1.1	-	0/6	Transient body weight loss.	DuPont, 1985a
(MW 730)	730 [cf]	1.0	-	0/6	Red nasal and/or ocular discharge.	
	2,200 [ce]	1.2	-	0/6	LC_{50} exceeds 5,100 mg/m^3.	
	4,200 [ce]	1.5	-	0/6		
	5,100 [ce]	1.4		0/6		
UCON 50-HB-260	3,870 [de]	6.7 - 6.9	5.1 - 5.3	0/10	Body weight loss. Red ocular discharge.	Union Carbide, 1988a
(MW 970)	4,430 [de]	6.0 - 6.4		0/10	Deaths 4-11 days after exposure. Dark discolouration of	
	4,920 [de]	6.4 - 7.9	5.0	7/10	lungs of decedents.	
			5.2 - 5.4		LC_{50} 4,770 mg/m^3 (4,260-5,350).	
UCON 50-HB-660	2,590 [del]	1.1	3.3	0/5	Increased respiratory rate and hypoactivity.	Klonne *et al*, 1987
(MW 1,700)	3,860 [del]	1.1	3.3	0/5	Deaths 4-5 days after exposure. Mottled lungs and liver	
	5,230 [del]	1.1	3.3	5/10	in decedents. LC_{50} 4,670 mg/m^3 (4,090-5,320)	
					for males and greater than 5,000 mg/m^3 for females.	
	200 [ce]	0.94	-	0/6	Red nasal and/or ocular discharge.	DuPont, 1985b
	2,900 [ce]	1.4	-	1/6	Body weight loss.	
	4,100 [ce]	1.5	-	1/6	LC_{50} approximately 4,500 mg/m^3.	
	5,400 [ce]	2.7	-	5/6		

* Chamber atmosphere concentrations determined by gravimetric analysis

[a] Mass median aerodynamic diameter of aerosol particles

[b] Geometric standard deviation of aerosol particles

[c] Nose-only exposure

[d] Whole-body exposure

[e] Aerosol generated from undiluted copolymer

[f] Aerosol generated from aqueous solution

[l] Copolymer heated to 55° to assist aerosol generation

APPENDIX A (continued 1): 4-HOUR [g] ACUTE INHALATION TOXICITY STUDIES IN RATS

Product (av. MW)	Atmosphere Concentration (mg/m^3)*	Aerosol Details		Mortality	Findings	Reference
		MMAD[a] (μm)	GSD[b]			
UCON 50-HB-2000	103 [df]	1.1	3.3	0/10	Deaths 2-5 days after exposure. Mottled lungs and livers in decedents.	Klonne *et al*, 1987
(MW 2,900)	412 [df]	1.1	3.3	6/10		
	992 [df]	1.1	3.3	10/10	LC_{50} 350 mg/m^3 (227-480).	
	300 [ce]	1.4	-	0/6	Body weight loss. Red nasal and/or ocular discharge.	DuPont, 1986a
	390 [ce]	1.8	-	3/6	Deaths 2-5 days after exposure.	
	470 [ce]	1.4	-	6/6	LC_{50} approximately 400 mg/m^3.	
	800 [ce]	2.5	-	6/6		
	1,900 [ce]	1.2		6/6		
UCON 50-HB-5100	94 [df]	1.3	3.3	3/10	Deaths 3-5 days after exposure. Mottled lungs and livers in decedents.	Klonne *et al*, 1987
(MW 4,000)	116 [df]	1.3	3.3	6/10		
	940 [df]	1.3	3.3	10/10	LC_{50} 106 mg/m^3 (45-245).	
	61 [cf]	1.2	-	1/6	Body weight loss. Red nasal and/or ocular discharge. Deaths 2-5 days after exposure. Haemorrhage and oedema of lungs.	DuPont, 1984
	92 [cf]	1.1	-	3/6		
	140 [cf]	1.2	-	6/6	LC_{50} approximately 100 mg/m^3.	
	210 [cf]	1.3	-	6/6		
	54 [df]	2.0 - 2.7	-	0/10	Deaths 4-6 days after exposure. Decreased body weight gain. Increased lung weight gain. Increased lung weight. Oedema, emphysema and discolouration of lungs. Congestion, oedema and haemorrhage of lungs. LC_{50} 147 mg/m^3 (116-185).	Hoffman *et al*, 1991
	100 [df]	2.0 - 2.7	-	9/10		
	200 [df]	2.0 - 2.7	-	3/10		
	500 [df]	2.0 - 2.7	-	10/10		
	36.3 [cf]	1.08	1.48	-	Exposure for variable times to attain required lung burdens. Animals sacrificed on day 4. Lung pathology.	ICI, 1992
	14.4 [cf]	1.08	1.48	-		
	113.3 [cf]	1.08	1.48	-		

* Chamber atmosphere concentrations determined by gravimetric analysis
[a] Mass median aerodynamic diameter of aerosol particles
[b] Geometric standard deviation of aerosol particles
[c] Nose-only exposure
[d] Whole-body exposure
[e] Aerosol generated from undiluted copolymer
[f] Aerosol generated from aqueous solution
[g] Except where otherwise stated

APPENDIX A (continued 2): 4-HOUR [g] ACUTE INHALATION TOXICITY STUDIES IN RATS

Product (av. MW)	Atmosphere concentration (mg/m^3)*	Aerosol Details MMAD[a] (μm)	Aerosol Details GSD[b]	Mortality	Findings	Reference
ICI copolymer (MW 4,000)	39.8 [cf]	0.68	2.87	Exposure for variable times to attain required lung burdens. Animals sacrificed on day 4. Body weight loss. Lung pathology.		ICI, 1992
	115.7 [cf]	0.68	2.87			
Pluracol W-5100 (MW 4,200)	91 [cf]			0/6	Body weight loss. Red nasal and/or ocular discharge. Deaths 3-5 days after exposure. LC_{50} approximately 150 mg/m^3.	DuPont, 1984
	92 [cf]	0.95	-	2/6		
	130 [cf]	0.96	-	1/6		
	200 [cf]	1.1	-	6/6		
	360 [cf]	1.5	-	6/6		
ICI copolymer (MW 4,500)	7.8 [cf]	0.80	1.54	Exposure for variable times to attain required lung burdens. Animals sacrificed on day 4. Body weight loss. Lung pathology.		ICI, 1992
	116 [cf]	0.80	1.54			
UCON 50-HB-5100R+ (MW 4,000)	80 [df]	0.8 - 1.6	1.8 - 6.1	0/10	Deaths after 3-8 days. Blepharospasm, body weight loss. Discolouration of lungs. LC_{50} 150mg/m^3 (100-230).	Union Carbide, 1990b
	120 [df]	0.8 - 1.6	1.8 - 6.1	5/10		
	370 [df]	0.8 - 1.6	1.8 - 6.1	10/10		
	740 [df]	0.8 - 1.6	1.8 - 6.1	10/10		
Water-initiated 50:50 random copolymer						
UCON 50-H-5100 (MW 4,000)	200 [df]	1.1 - 2.4	1.8 - 5.2	1/10	Deaths after 3-7 days. Decreased body weight gain. Discolouration of lungs, liver and kidneys. LC_{50} 340 mg/m^3 (230-520).	Union Carbide,1990c
	460 [df]	1.1 - 2.4	1.8 - 5.2	8/10		
	820 [df]	1.1 - 2.4	1.8 - 5.2	10/10		

* Chamber atmosphere concentrations determined by gravimetric analysis

[a] Mass median aerodynamic diameter of aerosol particles

[b] Geometric standard deviation of aerosol particles

[c] Nose-only exposure

[d] Whole-body exposure

[e] Aerosol generated from undiluted copolymer

[f] Aerosol generated from aqueous solution

[g] Except where otherwise stated

\+ Not commercially available

APPENDIX A (continued 3): 4-HOUR ACUTE INHALATION TOXICITY STUDIES IN RATS

Product (av.MW)	Atmosphere Concentration (mg/m^3)*	Aerosol Details MMAD[a] (μm)	Aerosol Details GSD[b]	Mortality	Findings	Reference
Butanol-initiated 75:25 Random Copolymer						
UCON 75-H-9500	40 [cf]	0.64	-	0/6	Red nasal discharge. LC_{50} >1,700 mg/m^3.	DuPont, 1985d
(MW not available)	1,200 [cf]	0.96	-	0/6		
	1,700 [cf]	1.1	-	0/6		
Water-initiated EO polymer						
UCON 75-H-380,000	860 [cf]	0.98	-	0/6	Transient body weight loss. Red nasal and/or ocular discharge. LC_{50} > 1,900 mg/m^3.	DuPont, 1985e
(MW »12,000)	1,500 [cf]	0.98	-	0/6		
	1,900 [cf]	1.0	-	0/6		
Water-initiated block copolymers						
Pluronic L31	180 [ce]	1.4	-	0/6	Transient body weight loss and noisy respiration. LC_{50} > 4,800 mg/m^3.	DuPont, 1985f
(MW 1,100)	4,800 [ce]	1.5	-	0/6		
Pluronic L64	40 [cej]	1.8	-	0/6	Transient body weight loss. Red nasal/ocular discharge and noisy respiration. LC_{50} > 1,500 mg/m^3.	DuPont, 1986b
(MW 2,900)	280 [cej]	2.7	-	0/6		
	1,500 [cej]	2.0	-	0/6		
Pluronic L81	710 [ce]	2.1	-	0/6	Red nasal/ocular discharge, respiratory effects. Deaths within 1 day of exposure. Body weight loss. LC_{50} approx. 2,000 mg/m^3.	Dupont, 1986b
(MW 2,750)	1,500 [ce]	2.0	-	0/6		
	2,400 [ce]	1.9	-	4/6		
	2,800 [ce]	1.7	-	6/6		

* Chamber atmosphere concentrations determined by gravimetric analysis

[a] Mass median aerodynamic diameter of aerosol particles

[b] Geometric standard deviation of aerosol particles

[c] Nose-only exposure

[e] Aerosol generated from undiluted copolymer

[f] Aerosol generated from aqueous solution

[j] Copolymer heated to 60-65° assist aerosol generation

APPENDIX A (continued 4): 4-HOUR ACUTE INHALATION TOXICITY STUDIES IN RATS

Product (av. MW)	Atmosphere Concentration (mg/m^3)*	Aerosol Details MMAD[a] (μm)	Aerosol Details GSD[b]	Mortality	Findings	Reference
Pluronic P84	1,500 [c]	-	-	0/6	Body weight loss.	Kennedy *et al*, 1990
(MW 4,200)	2,400 [c]	-	-	4/6	LC_{50} approx. 2,000 mg/m^3.	
	2,800 [c]	-	-	6/6		
Water-initiated EO-polymer						
PEG 200 (MW 200)	2,516 [deh]	0.78	-	0/12	No adverse reaction to exposure. LC_{50} exceeds 2,500 mg/m^3.	Crook *et al*, 1980a
Glycerol-initiated 50:50 random copolymer						
Polyglycol 15-200	1,000 [de]	1.6	2.3	0/10	No significant findings.	Dow Chemical, 1985
(MW 2,600)	2,000 [de]	1.6		0/10	LC_{50} exceeds 1,200 mg/m^3.	

* Chamber atmosphere concentrations determined by gravimetric analysis
[a] Mass median aerodynamic diameter of aerosol particles
[b] Geometric standard deviation of aerosol
[c] Nose-only exposure
[d] Whole-body exposure
[e] Aerosol generated from undiluted copolymer
[h] 6-hour exposure

APPENDIX B: ACUTE INHALTION TOXICITY STUDIES IN SPECIES OTHER THAN RAT [+]

Product (av. MW)	Species	Atmosphere Concentration (mg/m^3)*	Aerosol Details MMAD[a] (μm)	Aerosol Details GSD[b]	Mortality	Findings	Reference
Butanol-initiated 50:50 random copolymer							
UCON 50-HB- 5100 (MW 4,000)	Mouse	54 [c]	2.0 - 2.7	-	0/10	Deaths 3-5 days post-exposure.	Hoffman *et al*, 1991
		100 [c]	2.0 - 2.7	-	2/10	Concentration-related body weight loss,	
		200 [c]	2.0 - 2.7	-	8/10	increased lung weight and lung pathology.	
		500 [c]	2.0 - 2.7	-	10/10	LC_{50} 174 mg/m^3 (33-902).	
	Guinea pig	54 [c]	2.0 - 2.7	-	0/10	Deaths 4-5 days post-exposure.	
		100 [c]	2.0 - 2.7	-	0/10	Concentration-related body weight loss,	
		200 [c]	2.0 - 2.7	-	3/10	increased lung weight and lung pathology.	
		500 [c]	2.0 - 2.7	-	8/10	LC_{50} 293 mg/m^3 (216-397).	
	Hamster	54 [c]	2.0 - 2.7	-	0/10	Deaths 4-9 days post-exposure.	
		100 [c]	2.0 - 2.7	-	0/10	Concentration-related body weight loss,	
		200 [c]	2.0 - 2.7	-	0/10	increased lung weight and lung pathology.	
		500 [c]	2.0 - 2.7	-	5/10	LC_{50} 511 mg/m^3 (338-729).	
	Dog	52 [c]	2.0 - 2.7	-	0/2	Increased lung weight in highest exposure	
		91 [c]	2.0 - 2.7	-	0/2	group.	
		310 [c]	2.0 - 2.7	-	0/2	Concentration-related lung pathology.	
		450 [c]	2.0 - 2.7	-	0/2	LC_{50} greater than 450 mg/m^3.	

* Chamber atmosphere concentrations determined by gravimetric analysis

[+] Single 4-hour whole-body exposure except where indicated

[a] Mass median aerodynamic diameter of aerosol particles

[b] Geometric standard deviation of aerosol

[c] Aerosol generated from aqueous solution

APPENDIX B (continued 1): ACUTE INHALATION TOXICITY STUDIES IN SPECIES OTHER THAN RAT [+]

Product (av. MW)	Species	Atmosphere Concentration (mg/m^3)*	Aerosol Details MMAD[a] (μm)	Aerosol Details GSD[b]	Mortality	Findings	Reference
Water-initiated EO polymer							
PEG 200 (MW 190-210)	Mouse	2,516[df]	0.78	-	0/12	No adverse reaction to exposure. LC_{50} exceeds 2,500 mg/m^3.	Crook et al, 1980a
Octylphenol-initiated EO polymer							
TRITON X-100 (MW 647)	Hamster	3,000[e]	1.47	1.84	Exposure for variable times (nose only) to attain required lung burdens. Ulcerative laryngitis and laryngeal oedema; only minimal pulmonary changes. LC_{50} 1,700 μg (1,300-2,100), expressed in terms of initial lung burden.		Damon et al, 1982

* Chamber atmosphere concentrations determined by gravimetric analysis

[+] Single 4-hour whole-body exposure except where indicated

[a] Mass median aerodynamic diameter of aerosol particles

[b] Geometric standard deviation of aerosol particles

[d] Aerosol generated from undiluted copolymer

[e] Aerosol generated from solution in ethanol

[f] Single 6-hour whole-body exposure

APPENDIX C: SUMMARY OF SUB-ACUTE INHALATION TOXICITY STUDIES IN RATS [+]

Product (Av. MW)	Atmosphere Concentration (mg/m^3)*	Aerosol Details MMAD[a] (μm)	Aerosol Details GSD[b]	Findings	Reference
Butanol-initiated 50:50 random copolymer					
UCON 50-HB-260 (MW 970)	5 [d]	2.7	2.7	Reduced body weight gain. Haematology changes. Increased kidney weight. No effect on lung weight or lung pathology. NOEL 5 mg/m^3.	Tyler *et al*, 1990; Union Carbide, 1989a
	52 [d]	2.7	2.7		
	512 [d]	2.7	2.7		
				NOAEL 500 mg/m^3 for histopathological changes in the lung (see also Table 6, Section 7)	Lewis, 1995
UCON 50-HB-660 (MW 1,700)	504 [c]	3	3.2	Rats at 2,460 mg/m^3 died or were killed on days 4 to 10. Haematology and blood chemistry changes. Increased lung weights. Congestion, alveolar hisiocytosis, bronchopneumonia around blood vessels, and interstitial pneumonia. NOEL not established.	Klonne *et al*, 1989a; Union Carbide, 1988b
	982 [c]	3	3.2		
	2,460 [c]	3	3.2		
				LOAEL 500 mg/m^3 for histopathological changes in the lung (see also Table 6,Section 7) .	Lewis, 1995
	4.8 [c]	2.54	3.47	Haematology and blood chemistry changes. Reduced body weight gain. Increased lung and kidney weight. Intra-alveolar cellular debris, alveolar histiocytosis. NOEL 5mg/m^3.	Union Carbide, 1991
	50.6 [c]	2.54	3.47		
	97.7 [c]	2.54	3.47		
	492 [c]	2.54	3.47		

* Chamber atmosphere concentrations determined by gravimetric analysis (whole-body exposure)

[+] 9, 6-hour exposures, over 11 days

[a] Mass median aerodynamic diameter of aerosol particles

[b] Geometric standard deviation of aerosol particles

[c] Aerosol generated from aqueous solution

[d] Aerosol generated from undiluted polymer

APPENDIX C (continued 1): SUB-ACUTE INHALATION TOXICITY STUDIES IN RATS [+]

Product (av. MW)	Atmosphere Concentration (mg/m^3)*	Aerosol Details		Findings	Reference
		MMAD[a] (μm)	GSD[b]		
UCON 50-HB-2000 (MW 1,700)	42.3 [de]	1.3	-	1/24 rats died after 3 exposures. Increased lung weight. Pulmonary inflammation and transient substantial cytotoxicity, essentially normal after 7 days. NOAEL not established.	Warheit *et al*, 1995
	103 [d]	2.2	1.87	6/10 rats died after 3 exposures; remainder killed after 5 exposures. Increased lung weight. Congestion and haemorrhage of lungs. Alveolitis (oedema, haemorrhage and fibrin deposition). NOAEL not established.	Ulrich *et al*, 1992
UCON 50-HB-5100 (MW 4,000)	22.1 [de]	1.5 - 1.65	-	1/24 rats died after 3 exposures. Increased lung weight. Marked pulmonary inflammation and substantial cytotoxicity. Histopathology showed minimal inflamation persisting to 7 days. NOAEL not established.	Warheit *et al*, 1995
	4.8 [c] 25.5 [c] 49.5 [c]	1.5 1.5 1.5	2.7 2.7 2.7	Urinogenital wetness, unkempt appearance and nasal discharge. Reduced body weight gain. Haematology and blood chemistry changes. Increased lung weight. Congestion and haemorrhage in lungs, with necrosis and interstitial pneumonia. NOAEL not established.	Klonne *et al*, 1987
				NOAEL < 5 mg/m^3, LOAEL 5 mg/m^3 for histopathological changes in the lung (see also Table 6, Section 7).	Lewis, 1995
	55 [d]	2.3	0.13	9/10 rats died after 3 exposures, surviving animal killed after 5 exposures. Increased lung weight. Congestion and haemorrhage of lungs. Alveolitis oedema, haemorrhage and fibrin deposition. NOAEL not established.	Ulrich *et al*, 1992

* Chamber atmosphere concentrations determined by gravimetric analysis (whole-body exposure) unless otherwise specified

[+] 9, 6-hour exposures, over 11 days

[a] Mass median aerodynamic diameter of aerosol particles

[b] Geometric standard deviation of aerosol particles

[c] Aerosols generated from aqueous solution

[d] Aerosols generated from undiluted polymer

[e] Nose only exposure

APPENDIX C (continued 2): SUB-ACUTE INHALATION TOXICITY STUDIES IN RATS +

Product (av. MW)	Atmosphere Concentration (mg/m^3)*	Aerosol Details		Findings	Reference
		MMAD[a] (μm)	GSD[b]		
UCON 50-HB-5100 (MW 4,000)	0.9 [c]	2.2	1.8	Reduced body weight gain. Increased lung weight. Congestion and haemorrhagic foci in lungs. Alveolar histiocytosis, Type II pneumocyte hyperplasia. NOAEL not established.	Klonne *et al*, 1988
	5 [c]	2.2	1.8		
Water-initiated 75:25random copolymer					
UCON 75-H-1400 (MW 2,200)	111.7 [de]	1.8	-	Minor, transient pulmonary inflammation	Warheit *et al*, 1995
	191 [c]	2.3	1.83	Minimal alveolitis; macrophages had foamy cytoplasm LOAEL 200 mg/m^3 for histopathological changes in the lung (see also Table 6, Section 7).	Ulrich *et al*, 1992 Lewis, 1995
Water-initiated block copolymer					
Pluronic L31 (MW 1,100)	97 [d]	1.9	2.0	Minimal alveolitis; macrophages had foamy cytoplasm NOAEL 100 mg/m^3 for histopathological changes in the lung (see also Table 6, Section 7).	Ulrich *et al*, 1992 Lewis, 1995
	109.7 [de]	1.4 - 1.6	-	Minor, transient pulmonary inflammation	Warheit *et al*, 1995

* Chamber atmosphere concentrations determined by gravimetric analysis (whole-body exposures) unless otherwise specified

+ 9, 6-hour exposures, over 11 days

[a] Mass median aerodynamic diameter of aerosol particles

[b] Geometric standard deviation of aerosol particles

[c] Aerosol generated from aqueous solution

[d] Aerosol generated from undiluted polymer

[e] Nose-only exposure

APPENDIX C (continued 3): SUB-ACUTE INHALATION TOXICITY STUDIES IN RATS [+]

Product (av. MW)	Atmosphere Concentration (mg/m^3)*	Aerosol Details MMAD[a] (μm)	Aerosol Details GSD[b]	Findings	Reference
Pluronic L64 (MW 2,900)	99.3 [def]	2.6 - 1.7	-	Minor, transient pulmonary inflammation.	Warheit *et al*, 1995
	103 [d]	1.7	1.92	Minimal alveolitis; macrophages had foamy cytoplasm.	Ulrich *et al*, 1992
				LOAEL 100 mg/m^3 for histopathological changes in the lung (see also Table 6, Section 7).	Lewis, 1995
ICI Block Copolymer A (MW 4,000)	5 [c] 50 [c] 400 [c]	1.8 1.8 1.8	2.0 2.0 2.0	Reduced body weight gain and death at top concentration. Lung weight increase and dose-related inflammation and macrophage infiltration in the lung. Hypertrophy/hyperplasia at 400 mg/m^3. NOAEL not determined.	Allied Signal, 1993
				NOAEL < 5 mg/m^3, LOAEL 5 mg/m^3 for histopathological changes in the lung (see also Table 6, Section 7).	Lewis, 1995
Pluronic L122 (MW 12,000)	24 [d] 47 [d] 67 [d]	2.4 2.1 1.9	2.0 1.9 1.8	Concentration-related increases in lung weights.	Bio/dynamics, 1995
ICI Block Copolymer B (MW 12,000)	6.1 52 300	2.1 2.1 2.1	2.6 2.6 2.6	Increased lung weight with inflammation and macrophage infiltration at 300 mg/m^3. These effects seen to a lesser extent at 52 mg/m^3. NOAEL 6.1 mg/m^3.	Allied Signal, 1993
				NOAEL 5 mg/m^3, LOAEL 50 mg/m^3, for histopathological changes in the lung (see also Table 6, Section 7).	Lewis, 1995

* Chamber atmosphere concentrations determined by gravimetric analysis (whole-body exposure) unless otherwise specified

[+] 9, 6-hour exposures, over 11 days

[a] Mass median aerodynamic diameter of aerosol particles

[b] Geometric standard deviation of aerosol particles generation

[c] Aerosol generated from aqueous solution generation

[d] Aerosol generated from undiluted polymer

[e] Nose only exposure

[f] Copolymer heated to 40° C to assist aerosol

APPENDIX C (continued 4): SUB-ACUTE INHALATION TOXICITY STUDIES IN RATS +

Product (Av. MW)	Atmosphere Concentration (mg/m^3)*	Aerosol Details MMAD[a] (μm)	Aerosol Details GSD[b]	Findings	Reference
Water-initiated reverse block copolymers					
Pluronic 17R1 (MW 1,900)	102 [d]	1.8	1.97	Minimal alveolitis; macrophages had foamy cytoplasm. NOAEL 100 mg/m^3 for histopathological changes in the lung (see also Table 6, Section 7).	Ulrich *et al*, 1992 Lewis, 1995
Pluronic 31R1 (MW 3,700)	5.4 50 430	1.6 1.6 1.6	1.9 1.9 1.9	Reduced body weight gain and/or reduced food consumption at top conc. Dose related inflammation and macrophage infiltration in the lung. Hypertrophy/hyperplasia at 430 mg/m^3. NOAEL 5.4 mg/m^3 for females. No NOAEL for males.	Allied Signal, 1993
				NOAEL 50 mg/m^3, LOAEL 430 mg/m^3 for histopathological changes in the lung (see also Table 6, Section 7).	Lewis, 1995
Water-initiated EO polymer					
PEG 3350 (MW 3,350)	109 [c] 567 [c] 1,008 [c]	6.1 5.0 3.8	2.4 2.8 3.3	Reduced body weight gain and increased lung weight at top 2 exposure concentrations. Minimal to mild alveolar histiocytosis, considered to be a normal "low toxicity-dust" type response.	Klonne *et al*, 1989b

* Chamber atmosphere concentrations determined by gravimetric analysis (whole-body exposure)

\+ 9, 6-hour exposures, over 11 days

[a] Mass median aerodynamic diameter of aerosol particles

[b] Geometric standard deviation of aerosol particles

[c] Aerosol generated from aqueous solution

APPENDIX D: SUMMARY OF 13-WEEK INHALATION TOXICITY STUDIES

Product (Av. MW)	Atmosphere Concentration (mg/m^3)*	Aerosol Details MMAD[a] (μm)	Aerosol Details GSD[b]	Species	Findings	Reference
Butanol-initiated 50:50 random copolymer						
UCON 50-HB-5100 (MW 4000)	0.3 [c]	1.6	1.6	Rats	Decreased body weight gain at highest concentration. Haematology changes. Increased lung weight at all concentrations. Haemorrhage or areas or discolouration in lungs of rats at all concentrations. Haemorrhage and interstitial pneumonia (1.1 and 5.2 mg/m^3), alveolar histiocytosis and focal or multi-focal fibrosis. NOAEL not established.	Klonne *et al*, 1988
	1.1 [c]	1.6	1.6	Rats		
	5.2 [c]	1.6	1.6	Rats		
Water-initiated EO polymer						
PEG 200 (MW 200)	122 [d]	0.71	-	Rats and Mice	No exposure-related effects	Crook *et al*, 1980b
	101 [d]	0.80	-			

* Chamber atmosphere concentrations determined by gravimetric analysis (whole-body exposures; 6 h/d, 5d/w)

[a] Mass median aerodynamic diameter for aerosol particles

[b] Geometric standard deviation of aerosol particles

[c] Aerosol generated from aqueous solution

[d] Aerosol generated from undiluted polymer

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