Technical Report No. 55

Pulmonary Toxicity of Polyalkylene Glycols

December 1997

ISSN-0773-8072-55

Brussels, 1997

LIST OF ECETOC PUBLICATIONS (continued inside back cover)

MONOGRAPHS

No.	Title
No. 1	Good Laboratory Practice. Oct 79
No. 2	Contribution to Strategy for Identification and Control of Occupational Carcinogens. Sep 80
No. 3	Risk Assessment of Occupational Chemical Carcinogens. Jan 82
No. 4	Hepatocarcinogenesis in Laboratory Rodents : Relevance for Man. Oct 82
No. 5	Identification and Assessment of the Effects of Chemicals on Reproduction and Development (Reproductive Toxicology). Dec 83
No. 6	Acute Toxicity Tests. LD_{50}(LC_{50}) Determinations and Alternatives. May 85
No. 7	Recommendations for the Harmonisation of International Guidelines for Toxicity Studies. Dec 85
No. 8	Structure-Activity Relationships in Toxicology and Ecotoxicology: An Assessment. Feb 86
No. 9	Assessment of Mutagenicity of Industrial and Plant Protection Chemicals. Jun 87
No. 10	Identification of Immunotoxic Effects of Chemicals and Assessment of their Relevance to Man. Aug 87
No. 11	Eye Irritation Testing. Jun 88
No. 12	Alternative Approaches for the Assessment of Reproductive Toxicity (with emphasis on embryotoxicity/teratogenicity). Nov 89
No. 13	DNA and Protein Adducts: Evaluation of their Use in exposure Monitoring and Risk Assessment. Oct 89
No. 14	Skin Sensitisation Testing. Mar 90
No. 15	Skin Irritation. Jul 90
No. 16	Mutation Research. Special Issue: Early Indicators of Non-Genotoxic Carcinogenesis. Jun 91
No. 17	Hepatic Peroxisome Proliferation. May 92
No. 18	Evaluation of the Neurotoxic Potential of Chemicals. Sep 92
No. 19	Respiratory Allergy. Aug 93
No. 20	Percutaneous Absorption. Aug 93
No. 21	Immunotoxicity: Hazard Identification and Risk Characterisation. Sep 94
No. 22	Evaluation of Chemicals for Oculotoxicity. Nov 94
No. 23	Receptor Mediated Mechanisms in Chemical Carcinogenesis
No. 24	Risk Assessment for Carcinogens. Jul 96
No. 25	Practical Concepts for Dose Selection in Chronic Toxicity and Carcinogenicity Studies in Rodents. Jul 96
No. 26	Aquatic Toxicity Testing of Sparingly Soluble, Volatile and Unstable Substances. Feb 96
No. 27	Aneuploidy. Aug 97

JACC REPORTS

No.	Title
No. 1	Joint Assessment of Commodity Chemicals, Melamine. Feb 83
No. 2	Joint Assessment of Commodity Chemicals, 1,4-Dioxane. Feb 83
No. 3	Joint Assessment of Commodity Chemicals, Methyl Ethyl Ketone. Feb 83
No. 4	Joint Assessment of Commodity Chemicals, Methylene Chloride. Jan 84
No. 5	Joint Assessment of Commodity Chemicals, Vinylidene Chloride. Aug 85
No. 6	Joint Assessment of Commodity Chemicals, Xylenes. Jun 86
No. 7	Joint Assessment of Commodity Chemicals, Ethylbenzene. Aug 86
No. 8	Joint Assessment of Commodity Chemicals, Methyl Isobutyl Ketone. May 87
No. 9	Joint Assessment of Commodity Chemicals, Chlorodifluoromethane. Oct 89
No. 10	Joint Assessment of Commodity Chemicals, Isophorone. Sep 89
No. 11	Joint Assessment of Commodity Chemicals, (HFA-132b) 1,2-Dichloro-1,1-Difluoroethane. May 90
No. 12	Joint Assessment of Commodity Chemicals, (HFA-124) 1-Chloro-1,2,2,2-Tetrafluoroethane. May 90
No. 13	Joint Assessment of Commodity Chemicals, (HFA-123) 1,1-Dichloro-2,2,2-Trifluoroethane. May 90
No. 14	Joint Assessment of Commodity Chemicals, (HFA-133a) 1-Chloro-2,2,2-Trifluoromethane. Aug 90
No. 15	Joint Assessment of Commodity Chemicals, (HFA-141B) 1-Fluoro 1,1-Dichloroethane. Aug 90
No. 16	Joint Assessment of Commodity Chemicals, (HCFC-21) Dichlorofluoromethane. Aug 90
No. 17	Joint Assessment of Commodity Chemicals, (HFA-142b) 1-Chloro-1,1,Difluoroethane. Feb 91
No. 18	Joint Assessment of Commodity Chemicals, Vinylacetate. Feb 91
No. 19	Joint Assessment of Commodity Chemicals, Dicyclopentadiene. Jul 91
No. 20	Joint Assessment of Commodity Chemicals, Tris-/Bis-/Mono-(2-ethylhexyl)phosphate. May 92
No. 21	Joint Assessment of Commodity Chemicals, Tris-(2-butoxyethyl)-phosphate. Mar 92
No. 22	Joint Assessment of Commodity Chemicals, Hydrogen Peroxide. Jan 93
No. 23	Joint Assessment of Commodity Chemicals, Polycarboxylate Polymers as Used in Detergents. Nov 93
No. 24	Joint Assessment of Commodity Chemicals, (HFC-125) Pentafluoroethane. May 94
No. 25	Joint Assessment of Commodity Chemicals, (HCFC-124) 1-Chloro-1,2,2,2-Tetrafluoroethane. Jul 94
No. 26	Joint Assessment of Commodity Chemicals, Linear Polydimethylsiloxanes (viscosity 10-100,000 centistokes). Sep 94
No. 27	Joint Assessment of Commodity Chemicals, *n*-Butyl Acrylate. CAS No. 141-32-2. Aug 94
No. 28	Joint Assessment of Commodity Chemicals, Ethyl Acrylate. CAS No. 140-88-5. Sep 94
No. 29	Joint Assessment of Commodity Chemicals, 1,1-Dichloro-1-Fluoroethane (HCFC-141b) CAS No 1717-00-6. Feb 95
No. 30	Joint Assessment of Commodity Chemicals, Methyl Methacrylate. CAS No. 80-62-6. Feb 95
No. 31	Joint Assessment of Commodity Chemicals, 1,1,1 ,2-Tetrafluoroethane (HFC-134a) CAS No. 811-97-2. Feb 95
No. 32	Joint Assessment of Commodity Chemicals, Difluoromethane (HFC-32) CAS No. 75-10-5. May 95
No. 33	Joint Assessment of Commodity Chemicals, 1,1-Dichloro-2,2,2-trifluoroethane (HCFC-123) CAS No. 306-83-2.
No. 34	Joint Assessment of Commodity Chemicals, Acrylic Acid Cas No. 79-10-7. Sep 95
No. 35	Joint Assessment of Commodity Chemicals, Methacrylic Acid Cas No. 79-41-4. Mar 96

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).