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THE TOXICITY OF A RED PHOSPHORUS SMOKE AFTER REPEATED INHALATION

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Summary

Mice and rats were exposed to the smoke produced by ignition of a red phosphorus pyrotechnic composition, 1 h/d, 5d/week, at two different dose levels, together with controls. The mice received 180 exposures, while the rats received 200 exposures. Guinea pigs also underwent 200 exposures at the lower concentration, but all animals exposed at the higher concentration died during or immediately after the first dose. Growth of the test groups of mice and rats was depressed during the exposure period. Organ specific toxicity appeared not to be present in rats and was generally confined to the respiratory tract of the mice and the guinea pigs. A significantly higher proportion of the test group mouse lungs showed aggregates of macrophages containing granules than was present in the control group. Severe congestion was observed in practically all the lungs from the decedent high-dose group guinea pigs.

Introduction

Obscurant white smokes have a variety of civilian and military uses. Several types are available including those generated from zinc oxide/hexachloroethane mixtures [1–3], titanium dioxide/ hexachloroethane mixtures [4] and cinnamic acid [5,6]. Zinc oxide/hexachloroethane smokes have been shown to produce histological changes in the lungs of animals, including pulmonary oedema, alveolitis and fibrosis [2–4,7]. Furthermore, there have been numerous case reports of lung damage being produced by zinc oxide/hexachloroethane smoke in humans [8–15]. An alternative to zinc smokes, with, however, different military uses, is the ignition of phosphorus compositions: red phosphorus burns to phosphorus pentoxide and, when ignited in conditions of normal humidity, gives rise to a strongly hygroscopic aerosol consisting largely of orthophosphoric acid [16].

The acute inhalation toxicity of a red phosphorus smoke was studied by Ballantyne [17]. The 1-h LC_{50} was 271 (196–670) for the mouse, 1217 (970–1489) for the rat, 61 (52–80) for guinea pigs and 1689 (1200–3586) for rabbits (mg/m^3, with 95% confidence limits). Laryngeal and tracheal necrosis and

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acute inflammatory changes were seen in the decedents. In another study [18] rats and rabbits were exposed to single sublethal doses of one of two different red phosphorus smokes: rabbits killed at 24 h showed acute inflammation of the larynx and trachea and, in some cases, necrosis. Alveolitis was also seen. About half of those killed at 14 d showed laryngeal and tracheal inflammation, and all had some degree of alveolitis. Changes seen in the rats were similar and pulmonary congestion was also observed. The response to the two smokes, produced from the pyrotechnic compositions was similar. Despite these findings in the respiratory tracts of experimental animals, the use of red phosphorus smokes does not seem to have produced case reports of serious human poisoning. Nevertheless, as part of a continuing programme of study into the health effects of military smokes, we have investigated the repeated dose toxicity of a smoke produced from a red phosphorus pyrotechnic mixture.

Method

Animals

Three hundred 23-d old Porton-strain female mice, of mean weight 16.0 g, 150 41-d old Porton Wistar-derived female rats, of mean weight 113 g, and 138 41-d old Dunkin–Hartley female guinea pigs, of mean weight 350 g, were supplied by the Animal Breeding Unit, CDE Porton Down. The animals were randomly allocated into groups of approximately equal sizes, designated controls, low and high. This resulted in groups of 100 for the mice and 50 for the rats. The size of the dose groups of guinea pigs was 48 in the case of the control and low dose group, while there were 42 high dose group guinea pigs. Groups of animals were then subdivided. In the case of the mice, subdivision was into groups of ten to a cage, whilst the rats were divided into subgroups of five: the guinea pigs were similarly subdivided and housed as groups of six. Special precautions were not taken to prevent huddling, despite the possibility that this might reduce the inhaled dose. This was because a limited study suggests that huddling does not to affect the inhaled dose of toxicant, at least in the case of rats [19]. Between exposures, the animals were housed in special accomodation near to the inhalation unit, and then, after the last exposure, transferred to permanent accommodation.

Generation of the smoke

The pyrotechnic mixture was supplied by Dispersion Division, CDE. This mixture (Table 1) was in the form of granules. A measured amount of the material, the quantity depending on the desired concentration, was ignited with a fusee match in a static 10 m^3 chamber. To assist combustion a jet of air was blown over the burning pyrotechnic mixture.

TABLE 1

Composition of the pyrotechnic mixture

Amorphous oiled red phosphorus	95%
Polyvinyl butyral BL18	5%

Exposure

The animals were exposed to the freshly generated smoke, 1 h/d, 5d/week, until, in the case of the mice, they had experienced 180 exposures. Animals from the other two species underwent 200 exposures (i.e. 40 weeks; Table 2), except for the high-dose group of guinea pigs, all of which died during the exposure period. The high dose was one that was considered to be likely to produce definite toxicity in mice, but which, on a single dose basis, would be likely to be sublethal. The lower dose was intended to be about 1/8 of the high dose. Corresponding groups of each species were exposed together, starting with exposure of the controls to air within the chamber and ending with exposure of the high dose group. Because the concentration of smoke fell during exposure, the pyrotechnic mixture, in the form of fresh granules, was ignited to maintain the desired concentration. During the half-hour interval between exposure of the various dose groups, the chamber was thoroughly cleaned of detritis: at the end of the high dose exposure, the chamber was well-washed twice.

The smoke was sampled by drawing air at 5 l/min through GF/B filter papers. Filter papers were eluted into 40 ml of 1.25 *N* sulphuric acid. After filtration, a 4-ml aliquot was added to 5 ml 0.25% ammonium molybdate and 1 ml 0.06% hydrazine sulphate. This was mixed well, heated at 80 °C for 20 min and cooled and made up to 10 ml with 1.25 *N* sulphuric acid. The optical density of the resultant solution was read against a standard curve made using solutions of potassium dihydrogen phosphate in 1.25 *N* sulphuric acid. Eight samples of 5 min duration and 9 samples of 30 s duration were taken in the low and high dose exposures respectively. The impacted mass of smoke was weighed, allowing calculation of the concentration of solid material during exposure. Results were expressed as mg/m^3 phosphorus. The particle size of the smoke was not determined.

During the exposure period animals were examined for abnormal behaviour or ill-health. They were weighed weekly during exposure, and the mean whole body weight of each dose group of animals, relative to the mean weight of the corresponding controls was regressed against time. Animals showing clinical signs suggestive of ill-health were killed using sodium pentobarbital: those alive at the end of the study (19 months after the start of exposure) were similarly killed. Animals killed or found dead were examined post-mortem. At autopsy, lungs, larynx, trachea, liver , kidneys, spleen, thymus, mammary glands, sali-

TABLE 2

Concentration of smoke exposures, total dose received and duration and number of exposures during the study

Species	Dose-group	No. of animals	Exposures		Duration h	Number of exposures
			Conc[a] mg m^{-3}	Dose mg min m^{-3}		
Mice	Control	100	0	0	1	180
	Low	100	16.2 ± 4.3	175,222	1	180
	High	100	128.5 ± 29.8	1,388,080	1	180
Rats	Control	50	0	0	1	200
	Low	50	16.6 ± 9.8	199,504	1	200
	High	50	127.5 ± 38.5	1,530,274	1	200
Guinea-Pigs	Control	48	0	0	1	200
	Low	48	16.6 ± 9.8	199,405	1	200
	High	42	127.5 ± 38.5	–[b]	1	–[b]

[a] ± S.D. (as phosphorus).

[b] No guinea pig survived to the end of the exposure period in this group. Consequently the mean concentration represents the mean had they survived to 200 exposures.

vary glands and adrenals and thyroids, ovaries, heart, pancreas, oesophagus, stomach, small and large intestine were taken. In mice mesenteric lymph nodes were taken in addition to the above organs, while cervical lymph nodes were examined in the rats and guinea pigs. In rats, but not in the other two species, the pituitary gland, brain, uterus and a portion of skin were also examined microscopically. In the case of the high dose group guinea pigs, only the lungs were examined. Any other organ showing any macroscopical abnormality was also processed. After fixation in neutral buffered formalin, sections 5 ± 2 μm thick were cut and stained with haematoxylin and eosin. Histological data were recorded and analysed using a PLACES data acquisition system (Apoloco Ltd., 90 King Street, Newcastle-under-Lyme, England, ST5 1JB, UK). This package was run on a Micro VAX II minicomputer (Digital Equipment Corporation, Maynard, MA, U.S.A.).

Statistics

The number of decedents were insufficient for statistical analysis of histological data. Amongst the survivors, the frequency of histological changes in animals from the test groups was compared to that in the corresponding control groups, using Fisher's exact test. The mean weight of the test groups divided by the mean weight of the corresponding control group was regressed against time. The significance of the linear relationship was estimated from the ratio of the variances attributable to the regression compared to the residual (F-test).

Results

Exposure

The exposure concentrations were close to the anticipated concentrations of 15 and 130 mg/m^3.

Survival

The study was remarkable for the high decedency in many groups (Table 3). Thus, in the case on the mice, more than 50% died in each dose group during the study. However, in this species, a smaller number of controls died than in the low-dose group (59% versus 63%). On the other hand there appeared to be a clear excess of deaths in the high-dose group, in which about 80% died. Among the rats, death rats were similar in the three dose groups, while in the guinea pigs, 15% and 38% died before the end of the experiment in the control and low-dose group respectively. All guinea pigs in the high-dose group died during or immediately after the first exposure.

Growth

The weight of the low-dose group mice, relative to the controls, decreased during exposure, especially over the first 40 days ($P<0.05$). A greater, more consistent and more significant fall was seen in the high-dose group mice throughout the exposure period ($P<0.001$). The relative weights of both test groups of rats fell throughout the exposure period, at a somewhat higher rate in the case of the high-dose group animals than in the low-dose group (Fig. 1). In the case of both groups, statistically significant relationships were revealed ($P<0.001$). The relative weight of the low-dose group of guinea pigs rose during exposure.

TABLE 3

Numbers of animals dying before completion of the study

Species	Dose-group	Total dying		Total number of animals in group
		During study	During exposure	
Mice	Control	59	24	100
	Low	63	21	100
	High	78	45	100
Rats	Control	13	1	50
	Low	12	2	50
	High	10	1	50
Guinea-Pigs	Control	7	3	48
	Low	18	10	48
	High	42	42	42

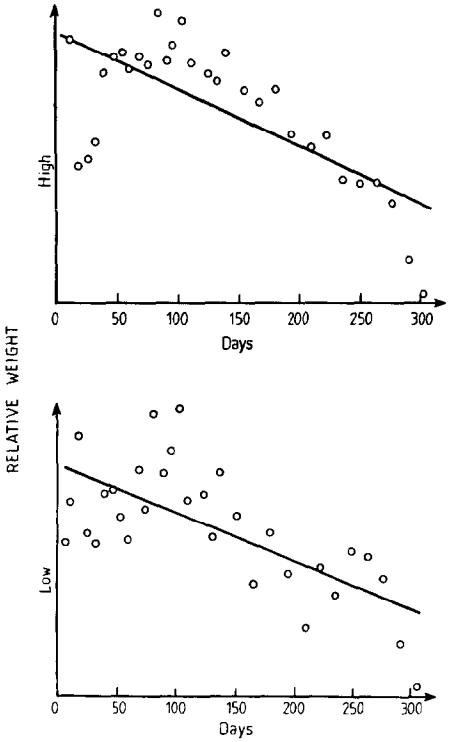

Fig. 1. Mean weight of test groups of rats relative to the controls during exposure.

Early deaths

Twenty control mice, 7 of which died during exposure had microscopic appearances consistent with severe chronic murine pneumonia. A further two had a milder form of the same condition. In some animals aggregations of macrophages were seen in the alveoli or bronchioles. Alveologenic carcinoma was not seen in the lungs from decedents of this group. One (thymic) lymphoma was seen in an animal dying during the observation period, as well as a uterine sarcoma in another mouse. Several animals showed salivary gland abscesses. Among the low dose group decedents, histopathological appearances were generally similar. Thirty out of 63 animals had severe chronic murine pneumonia, with a similar proportion being affected in those dying during exposure and those dying during subsequent observation. A further 3 had a milder form of the same changes. In many of the animals aggregates of macrophages were seen in the alveoli and/or bronchioles. One alveologenic carcinoma was seen in an animal dying during the observation period. Four lymphomas were seen, none involving the thymus. In two cases lymphomatous infiltration was seen only in the lymph nodes, while in another the liver was additionally affected. The fourth lymphoma involved lymph nodes, liver and spleen. Although there were

many decedents in the high dose group, histological appearances were similar to the other groups. Severe chronic murine pneumonia was observed in 36 out of 78 mice, while three had the less severe form of the same changes. As in the other groups, macrophage aggregations were often seen in the alveoli or bronchioles. Neither alveologenic carcinoma nor lymphoma was seen in the high dose group decedents.

Among the decedent rats, these was only one animal, a rat with pyelonephritis, that died during the exposure period in the control group. Those controls dying during the observation period had lungs free from significant histological abnormalities. However, in this group, there was a single case of focal hepatic necrosis and two of focal portal fibrosis. Twelve animals showed evidence of rat nephropathy, while 4 fibroadenomas of the mammary glands were seen. Furthermore, there was an adrenal cortical adenoma and a pituitary adenoma. Histological changes in the low-dose group animals were similar: two died during the exposure period, with focal portal fibrosis and acute pyelonephritis respectively. One animal dying during the observation period had emphysema, while 3 had evidence of lymphomatous infiltration in the lung and the liver. In one instance this infiltration was additionally present in the kidneys and adrenal gland: in another, lymphomatous infiltration was also present in the spleen. Rat nephropathy was common as in the controls, but only one fibroadenoma and one fibroma of the mammary gland was seen. In the high dose group, very mild pulmonary oedema was observed in a single animal dying during exposure, while foam cells were present in the lungs of another. Two decedents showed portal fibrosis, one exhibited acute pyelonephritis and a fibroadenoma of the mammary gland was seen. Additionally there was one squamous cell carcinoma of the skin and 4 pituitary adenomas.

Lymphoid foci were frequent in decedent guinea pigs of all groups. Interstitial nephritis was also common. Among the control animals, one showed aggregates of macrophages in the lungs, while another had focal necrosis of the liver. In the low-dose group, pulmonary oedema was seen in two guinea pigs dying during the exposure period and a lung abscess in a third. Bile duct hyperplasia, an abscess in the abdominal cavity and a uterine fibroid were each seen on single occasions in animals dying during the observation period. At autopsy of the high-dose group guinea pigs, which all died in the first day of the study (see above), only the lungs were taken for histological processing and study. Macroscopically, there was haemorrhage and collapse, while microscopically there was severe congestion with in some instances mild to moderate oedema.

Survivors

Histological changes observed in mice that survived to the end of the experiment are shown in Tables 4–6. Abnormalities were not seen in the mammary glands, pancreas, thyroid, oesophagus, duodenum, jejunum, ileum and colon,

TABLE 4

Selected histological changes seen in mouse survivors after exposure to the smoke

Organ and histological change	Dose group		
	Control (41)[a]	Low (37)	High (22)
Lung			
Alveologenic carcinoma	2	5	2
Alveolar aggregates of macrophages with granules	2	9[b]	9[c]
Bronchiolar aggregates of macrophages with granules	13	8	5
Interstitial pneumonitis	1	4	3
Bronchiectasis	1	1	1
Perivascular lymphocytic infiltration	10	20	10
Peribronchial lymphocytic infiltration	33	27	17
Larynx			
Epithelial lymphocytic infiltration	29	25	20
Intraluminal pus	1	0	0
Trachea			
Epithelial lymphocytic infiltration	10	1[d]	3
Lymph nodes (mesenteric)			
Lymphoma	0	1	0
Thymus			
Lymphoma	0	3	0
Heart			
Focal arteritis	0	1	1
Liver			
Perivascular lymphocytic infiltration	0	2	0
Periportal lymphocytic infiltration	0	1	0
Hepatoma	1	0	0
Hepatocellular carcinoma	1	0	0
Spleen			
Lymphoid hyperplasia	0	1	0
Kidneys			
Lymphocytic infiltration	29	18	10
Chronic interstitial nephritis	0	2	1
Adrenals			
Lymphocytic infiltration	0	1	0
Non-Protocol organs,			
Cervical lymph nodes			
lymphoma	0	3	0

[a]Group size.

[b] $P < 0.05$: significantly more frequent in test group than controls.

[c] $P < 0.001$: significantly more frequent in test group than controls.

[d] $P < 0.05$: significantly less frequent in test group than controls.

TABLE 5

Selected histological changes seen in rat survivors after exposure to the smoke

Organ and histological change	Dose group		
	Control (37)[a]	Low (38)[a]	High (40)[a]
Lung			
Alveolitis	4	5	3
Peribronchiolar lymphocytic infiltration	32	37	36
Perivascular lymphocytic infiltration	16	17	22
Oedema	0	0	2
Emphysema	0	2	1
Larynx			
Submucosal lymphocytic infiltration	1	1	0
Trachea			
Submucosal lymphocytic infiltration	1	0	0
Mammary Glands			
Lipoma	0	0	1
Fibroadenoma	2	1	1
Duct ectasia	5	5	3
Thyroid			
Cystic changes	4	4	7
Liver			
Nodular hyperplasia	1	3	0
Focal periportal fibrosis	12	14	16
Pancreas			
Arteritis	1	1	0
Spleen			
Megakaryocytopoesis	0	2	0
Kidneys			
Nephropathy	29	20[b]	20[b]
Interstitial lymphocytic infiltration	19	8[b]	5[b]
Nephrocalcinosis	8	6	2[b]
Adrenal			
Nodule	0	2	1
Medullary haemorrhage	6	7	8
Pituitary			
Adenoma	1	1	5
Uterus			
Adenomatous polyp	0	0	1
	0	0	1
	2	0	0

[a]Group size.

[b]Significantly less frequent than controls ($P < 0.05$).

TABLE 6

Selected histological changes seen in guinea pig survivors after exposure to the smoke

Organ and histological change	Dose group	
	Control (41)[a]	Low (30)[a]
Lung		
Peribronchiolar lymphocytic infiltration	1	1
Perivascular lymphocytic infiltration	30	29
Pleural thickening	1	0
Alveolar macrophages	1	0
Congestion	41	29
Bronchopneumonia	1	1
Abscess	1	0
Mammary gland		
Lipoma	0	1
Heart		
Scarring (focal)	1	0
Liver		
Focal necrosis	2	0
Biliary hyperplasia	1	0
Patchy fibrosis	1	0
Pancreas		
Islet cell adenoma	0	1
Kidney		
Chronic interstitial nephritis	17	21[b]
Nephrocalcinosis	20	22
Ovary		
Serous cyst	16	20
Non-protocol organs,		
Gall bladder		
Cholecystitis	1	0

[a]Group size.
[b]Significantly more frequent in test animals ($P < 0.05$).

while all stomachs examined, except for one from a high-dose animal, were normal. The exception showed ulceration. In the salivary glands, one instance of lymphocytic infiltration and of a cyst could be seen, both in animals from the control group. Lymphomas were seen only in the low-dose group, where there were three. All were of thymic origin and additionally involved the cervical lymph nodes. In one case the mesenteric nodes that were examined were also affected.

There were no dose-related changes in the rat lungs: in all groups of rats, a high proportion had pulmonary collapse and congestion. Two animals, from the high-dose group, had intra-alveolar oedema. Most extra-respiratory organs

were normal, including the heart, lymph nodes, salivary glands, urinary bladder, skin, oesophagus, stomach, duodenum, jejunum, ileum and colon, and brain. All ovaries were normal except for one from a control animal with a serious cyst.

Since no high-dose group animal survived the study, histological changes observed in guinea pig tissues were only analyzed statistically in case of the controls and low-dose group. The prevalence of histological changes in the two groups was similar in both respiratory and extra-respiratory organs. A possible exception was the frequency of chronic interstitial nephritis, which was significantly more common in the low dose group ($P < 0.05$). Among the incidental findings, lymphoid nodules were seen in the lungs of the survivors, as in the decedents. No histopathological abnormality was observed in the trachea, larynx, salivary or adrenal glands or in the thyroid, thymus, spleen or gut (oesophagus, stomach, duodenum, jejunum, ileum, colon). Among the non-protocol organs, two control gall bladders were abnormal, one with acute cholecystitis and one with chronic cholecystitis. Two control urinary bladders had squamous metaplasia. One from the control group and one from the low-dose group had chronic inflammatory changes.

Discussion

There was a marked species difference in tolerance to the smoke; rats were most resistant, guinea pigs least and mice occupied an intermediate position. Similar species differences have been observed in previous studies, although the death rate in the high-dose guinea pigs, in the present study, was exceptional [3,6,19–22]. The concentrations used here represent, in mice, less than one half and 1/17 of the single dose LC_{50} reported by Ballantyne [17] for the high and low dose groups. In the rats the concentrations used in the present experiment were equal to 1/10 and 1/75 of the LC_{50}. On the other hand Ballantyne [17] reported a single dose LC_{50} in guinea pigs which was less than half the high concentration used in the present study. The favourable survival figures observed in rats and the high mortality in the high-dose group of guinea pigs is thus readily explicable. Thus the use of a high dose that was, as intended, toxic to mice but also sublethal, produced death in guinea pigs and hardly affected the rats. This was, of course, the consequence of using the same exposure concentrations in the three species. The survival figures in the present study are rather more difficult to compare with the sublethal study in rats [18], because in that study the duration of exposure was only 30 min. In that study a total of 5 out of 30 rats, exposed to two different concentrations of red phosphorus smokes, died.

Except in the case of the guinea pigs, growth was reduced in all the test animals, Moreover, it was not possible to demonstrate a no-effect-dose for

depression of growth. Furthermore, the smoke affected survival in the mice and the guinea pigs. By contrast, rat survival was unaffected.

With the exception of the high-dose group guinea pigs, decedents mostly failed to show pathological changes, either in the respiratory tract or elsewhere, likely to have been a consequence of exposure to the test material. On the other hand the high-dose guinea pigs, all of whom died during or just after the first exposure, showed pulmonary congestion accompanied, in some cases, by haemorrhage and collapse, all of which were undoubtedly responses to the smoke. In all species the scanty changes seen in survivors mostly appeared to be incidental. An exception was the observation of aggregations of macrophages found in lungs of the test groups of mice. These have been described in previous repeated dose studies in which military smokes were tested [3], and may, in part, be caused by secondary infection. Histological changes related to the test material were not seen in the rats or surviving guinea pigs and the absence of such signs may have been due to the long observation period.

Incidental findings of interest, in the present study, included renal disease in all three species: chronic interstitial nephritis was seen in the mice and guinea pigs and nephropathy in the rats [23–26]. A number of alveologenic carcinomas was observed in mice, but this finding was not frequent and there was no indication of a dose response in the prevalence of the tumour in the different groups: no attempt was made to separate these neoplasms into benign and malignant as is sometimes done [27], and the criteria for histopathological diagnosis were those of Stewart et al. [28,29]. The presence of lymphoid nodules, seen in the lungs of both decedent and surviving guinea pigs, is well-recognised as a frequent incidental finding of unknown origin, in this species [30,31].

Despite the fact that red phosphorus smoke is largely an aerosol of orthophosphoric acid, which has a pK_a of about 2, for its first proton [32], specific damage to the respiratory tract has only rarely been seen in the present study. If, at the end of exposure, damage was present, it had been reversed by the end of the observation period. This suggests that delayed and incompletely reversible changes, similar to those seen in animal studies of the toxicity of zinc oxide/hexachloroethane smoke, are unlikely to occur with phosphorus smokes. Assuming that the experimental animal data correlate with human experiences, with both smokes, the latter is much less likely to give rise to long term respiratory impairment than the former. On the other hand, the very marked species differences in lethality, observed in the present study, must indicate caution in quantitative extrapolation to humans of the study data, reinforced as they are by major differences in acute lethality figures [17]. Thus there would be considerable difficulties in producing exposure limits for the use of the smoke, from present and past lethality data [17,18]. Whilst it is reasonable to assume that the guinea pig death rate is due to the peculiar sensitivity of that species to irritant aerosols [33], no similar explanation can be supplied

for the discrepancy between the lethality observed in the mouse and rat, nor are there data on which to base a choice of the most suitable species for extrapolation to man. A threshold limit value-time weighted average (TWA) of 1 mg/m^3 and a short term exposure limit (STEL) of 3 mg/m^3 has been adopted for phosphoric acid by the American Conference of Governmental Industrial Hygienists [34]. The TWA, which is, of course, for an 8 h exposure, is difficult to compare with the present study, since it is designed for pure phosphoric acid. By contrast the smoke used in the present study is likely to contain many compounds in addition to orthophosphoric acid [16]. Such compounds might include cyclotetraphosphoric and other polyphosphoric acids, as well as small amounts of phosphine, produced from phosphorus trioxide.

References

1 A. Jarvis, The combustion reactions of a pyrotechnic white smoke composition, Combustion and Flame, 14 (1970) 314-320.
2 T.C. Marrs, W.E. Clifford and H.F. Colgrave, Pathological changes produced by exposure of rabbits and rats to smokes from mixtures of hexachloroethane and zinc oxide, Toxicol. Lett., 19 (1983) 247-252.
3 T.C. Marrs, H.F. Colgrave, J.A.G. Edginton, R.F.R. Brown and N.L. Cross, The repeated dose toxicity of a zinc oxide/hexachloroethane smoke, Arch. Toxicol., 62 (1988) 123-132.
4 N. Karlsson, G. Cassel, I. Fängmark and F. Bergman. A comparative study of the acute inhalation toxicity of smoke from TiO_2-hexachloroethane and Zn-hexachloroethane pyrotechnic mixtures, Arch. Toxicol., 59 (1986) 160-166.
5 B. Ballantyne and W.E. Clifford, Short-term inhalation toxicology of cinnamic acid smoke, J. Combust. Toxicol., 5 (1978) 253-260.
6 T.C. Marrs, H.F. Colgrave, J.A.G. Edginton and N.L. Cross, Repeated dose inhalation toxicity of cinnamic acid smoke, J. Hazardous Mater., 21 (1989) 1-15.
7 R.F.R. Brown, T.C. Marrs, P. Rice and L.C. Masek, The histopathology of rat lung following exposure to zince oxide/hexachloroethane smoke or instillation with zinc chloride followed by treatment with 70% oxygen. Environ. Health Perspect., in press.
8 C.M.B. Pare and M. Sandler, Smoke bomb pneumonitis: description of a case, J. Royal Army Med. Coll., 100 (1954) 320-322.
9 F.A. Johnson and R.B. Stonehill, Chemical pneumonitis from inhalation of zinc chloride. Dis. Chest. 40 (1961) 619-624.
10 J.A. Milliken, D. Waugh and M. Kadish, Acute interstitial pulmonary fibrosis caused by a smoke bomb. Can. Med. Assoc. J., 88 (1963) 36-39.
11 M.B. Macaulay and A.K. Mant, Smoke bomb poisoning — A fatal case following the inhalation of zinc chloride smoke. J. Royal Army Med. Coll., 110 (1964) 27-32.
12 K.U. Helm, H.-D. Renovanz, K. Schmahl and M. von Clarmann, Die Zinknebelvergiftung und ihre Behandlung. II. Symptomlogie und Verlauf der Vergiftungen, Wehrmed. Monatschr., 15 (1971) 203-217.
13 H. Fischer, Morphologie der Zinknebelvergiftung der Lunge, Pneumologie, 150 (1954) 171-172.
14 M.B. Schenker, F.E. Speizer and J.O. Taylor, Acute upper respiratory symptoms resulting from exposure to zinc chloride aerosol, Environ. Res. 25 (1981) 317-324.
15 S.L. Matarese and J.I. Matthews, Zinc chloride (smoke bomb) inhalational lung injury, Chest, 89 (1986) 308-309.

16 F.G. Burton, M.L. Clark, R.A. Miller and R.E. Schirmer, Generation and characterisation of red phosphorus smoke aerosols for inhalation exposure of laboratory animals. Am. Ind. Hyg. Assoc. J., 43 (1982) 767–772.
17 B. Ballantyne, Acute inhalation toxicity of phosphorus pentoxide smoke, Toxicologist, 1 (1981) 140.
18 T.C. Marrs, Histological changes produced by exposure of rabbits and rats to smokes produced from red phosphorus, Toxicol, Lett., 21 (1984) 141–146.
19 T.C. Marrs, H.F. Colgrave and N.L. Cross, A repeated dose study of the toxicity of technical grade dibenz-(b.f.)-1,4 oxazepine in mice and hamsters, Toxicol. Lett., 17 (1983) 13–21.
20 T.C. Marrs, H.F. Colgrave, N.L. Cross, M.F. Gazzard and R.F.R. Brown, Repeated dose inhalation toxicology of CS (2-chlorobenzylidene malononitrile) in three species of laboratory animal, Arch. Toxicol., 52 (1983) 183–198.
21 T.C. Marrs, H.F. Colgrave, M.F. Gazzard and R.F.R. Brown, Inhalation toxicity of a smoke containing solvent yellow 33, disperse red 9 and solvent green 3 in laboratory animals, Human Toxicol., 3 (1984) 289–308.
22 T.C. Marrs, H.F. Colgrave, N.L. Cross, J.A.G. Edginton and B.C. Morris, Inhalation toxicity of a coloured smoke and the mutagenicity of its constituent dyes, Solvent Yellow 33 (CI 47000) and Disperse Orange 11 (CI 60700) in the Ames test, J. Hazardous Mater. 17 (1988) 269–285.
23 W. Andrew and D. Pruett, Senile changes in the kidney of Wistar institute rats, Am. J. Anat., 100 (1957) 51–80.
24 H.W. Casey, K.M. Ayers and F.R. Robinson, The urinary system, In: K. Bernischke, F.M. Garner and T.C. Jones (Eds.), Pathology of laboratory animals, Vol. 1. Springer-Verlag, New York, NY, 1979, p. 116.
25 P. Greaves and J.M. Faccini, Rat Histopathology, A Glossary for Use in Toxicity and Carcinogenicity. Elsevier, Amsterdam, 1984, p. 144.
26 K.C. Snell, Spontaneous lesions of the rat, in: W.E. Ribelin and J.R. McCoy (Eds.), The Pathology of Laboratory Animals. Charles C. Thomas, Springfield, IL, 1965, p. 241.
27 J.R. Glaister, Principles of toxicological pathology. Taylor and Francis, London, 1986, pp. 198–199.
28 H.G. Grady and H.L. Stewart, Histogenesis of induced pulmonary tumors in strain A mice, Am. J. Pathol., 16 (1940) 417–432.
29 H.L. Stewart, T.B. Dunn, K.C. Snell and M.K. Deringer, Tumours of the respiratory tract, In: WHO Monographs on the Pathology of Tumours of Laboratory Animals, Vol. 1. The Mouse. International Association for Research on Cancer (IARC), Lyons, France, 1979, p. 251.
30 J.E. Wagner, Miscellaneous disease conditions of guinea-pigs, in: J.E. Wagner and P.J. Manning (Eds.), The Biology of the Guinea-pig. Academic Press, New York, NY, 1976, pp. 228–234.
31 A. Baskerville, A.B. Dowsett and M. Baskerville, Ultrastructural studies of chronic pneumonia in guinea-pigs, Lab. Animals. 16 (1982) 351–355.
32 A. Albert, Selective Toxicity, 6th ed. Chapman and Hall, London, 1979, p. 335.
33 R.H. Hoar, Toxicology and teratology, in: J.E. Wagner and P.J. Manning (Eds.), The Biology of the Guinea-pig. Academic Press, New York, NY, 1976 pp. 269–280.
34 American Conference of Governmental Industrial Hygienists. Threshold limit values and biological exposure indices for 1987–1988. ACGIH, Cincinnati, Ohio.