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ENVIRONMENTAL HEALTH CONTROL FOR THE RUBBER INDUSTRY, PART II

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VII. ANTIOXIDANTS AND ANTIOZONANTS

This is the last of a two-part presentation, the first having appeared a year ago[1]. Part I dealt with the health control relating to polymer manufacturing, processing chemicals, and accelerators. Part II is confined to a discussion of antioxidants and antiozonants. While an attempt has been made to review the known toxicology and handling experience of the commercially-used antioxidants and antiozonants, there undoubtedly have been inadvertent omissions from the list.

1. *Aldol—α-naphthylamine (Agerite Resin).*—This compound has received clearance by the U. S. Food and Drug Administration for use in rubber articles with repeated food contact[2].

2. *Alkylated phenols*[2].—This is a group of four antioxidants of unspecific chemical structure and not otherwise classified in this presentation: Nevastain A, Nevastain B, Cyanox LF, and Santowhite 54.

Nevastain A has an oral LD_{50} for rats of 1.7 g/kg, while that for Nevastain B is approximately 20 g/kg[3]. Cyanox LF possesses an oral LD_{50} for the rat of 2.47 g/kg, a dermal LD_{50} for the rat of >50 g/kg, and a dermal LD_{50} for the rabbit in excess of 12.6 g/kg[5]. Eye irritation studies, using rabbits, of Cyanox LF and Santowhite 54 showed a slight to negative effect when instilled undiluted into rabbits' eyes[4,5].

None of these antioxidants presents any unusual handling requirements. The past history of usage has been quite favorable.

3. *N,N'-Bis(1,4-dimethylpentyl)-p-phenylenediamine (Eastozone 33).*—Experimental studies by the Eastman Kodak Co.[6] show that rats are killed with single oral doses of 1.6 g/kg and with single intraperitoneal doses of 0.8 g/kg, while similar routes of administration for mice produced deaths at levels of 0.8 g/kg and 0.4 g/kg, respectively. Deaths were delayed, up to twelve days. Some slight irritation to the skin of guinea pigs occurred with 24 hour contact of 0.1–5 ml/kg of the undiluted product, but there was no evidence of systemic effects. Some slight sensitizing effect to guinea pig skin was observed.

These data indicate no serious acute health problems should be expected and actual use of the compound over a number of years has confirmed this. Skin contact should be minimized.

4. *N,N'-Bis(1-ethyl-3-methylpentyl)-p-phenylenediamine (UOP 88).*—The UOP Chemical Company has carried out various toxicological studies on its product. These show that it has an oral LD_{50} for rats of 2400 mg/kg and an

LD_{50} of 900 mg/kg. Its percutaneous toxicity for rabbits showed an LD_{50} of 1800 mg/kg and an LD_0 of 45 mg/kg. Acute inhalation studies, using rats and guinea pigs and using exposures of atomized UOP 88 for 1 h, showed no effects at 30 ppm for rats and 37.5 ppm for guinea pigs. A similar exposure after a 1 week waiting period showed no further effects, including any sensitization[7]. Draper and Johnson[8] have fed this compound to pregnant rats over an approximately 2-month period at dietary levels of 0.025%, 0.1%, and 0.4%. Marked retardation of growth occurred at the highest level. No effect on reproduction was observed at the lowest level, and perhaps not at the intermediate level, although the results were not entirely clear. Histopathology for all levels was negative.

Repeat insult patch tests using 50 humans (application of the test product was made to the same site for a 24 h period every other day) showed the compound was not a primary irritant but a sensitizer. Similar tests, using a rubber compound containing 3 parts of UOP 88 per 100 parts of rubber, showed no primary irritation and no sensitization[7].

The rubber industry's experience in the use of this compound has been favorable. It should be regarded as a skin sensitizer and skin contact should, therefore, be prevented.

5. *N,N'-Bis(1-methylheptyl)-p-phenylenediamine (UOP 288).*—Draper and Johnson have fed four dietary levels to pregnant rats ranging from 0.005% to 0.4% for two months[8]. Adverse effects on growth rate, as well as litter size, were observed at 0.1% and 0.4%. No other adverse effects, either grossly or histopathologically, were observed.

6. *6-tert-Butyl-m-cresol and sulfur dichloride reaction product (Santowhite MK).*—This antioxidant is a dark liquid with no specific chemical structure. The manufacturer, The Monsanto Company, has performed some preliminary toxicological studies[5]. These indicate an oral LD_{50} for the rat of 17.5 g/kg. The minimal single lethal dose, when applied to the skin of rabbits, was >10 g/kg; a moderate amount of skin irritation resulted. In undiluted form it is definitely an eye irritant. Rats have been exposed for an 8 h period to vapors generated by heating it to 120° C with only slight nasal irritation resulting.

In using this product, care should be taken to prevent any entrance into the eye. If accidental contact should occur, prompt washing for a minimum of 15 min with water should be done and then prompt referral to a physician. Skin contact should be avoided.

7. *N-sec-Butyl-N'-phenyl-p-phenylenediamine (Flexzone 5L).*—There is no reported experimental toxicology. It is known to be a skin sensitizer with some individuals. Handling experience in the rubber industry has been favorable.

8. *N-Buty-p-aminophenol (Tenamene 1).*—The Tennessee Eastman Company has observed an LD_{50} of >5 ml/kg by percutaneous absorption with guinea pigs. These same studies indicated a moderate degree of skin irritation[9].

This compound is recognized as a potential skin irritant and handling procedures in industry should be designed to prevent skin contact.

9. *4,4'-Butylidene-bis(6-tert-butyl-m-cresol) (Santowhite Powder)*[2].—The Monsanto Company has observed an acute oral, minimum lethal dose for rats of 17 g/kg. Rats have been fed diets containing 500 ppm for 90 days and showed no signs of toxicity. Dermatological studies performed on human volunteers indicate that this compound is not a primary irritant nor a sensitizer[5].

The history of use in the rubber industry has been quite favorable. No special handling precautions are needed.

10. *Catechol (pyrocatechol; 1,2-dihydroxybenzene)*.—This old chemical compound has considerable toxicological background[11]. Its principal effect is on the central nervous system, like phenol. However, its acute toxicity, based upon animal data, is higher than phenol. The approximate acute lethal oral doses for animals are: dog, 0.13 g/kg; cat, 0.1 g/kg; rabbit, 0.2 g/kg; and guinea pig, 0.16 g/kg[12].

It is readily absorbed through the skin and skin irritation has been reported[12]. In general, the industrial experience in using catechol has been good. However, its hazards must be recognized and appropriate steps taken to prevent inhalation and skin exposures.

11. *Butylated-octylated phenols (Wingstay T)*.—The Goodyear Tire and Rubber Company has performed experimental toxicology with this compound[13]. Rats have been fed five dietary levels, ranging from 5 to 500 mg/kg of body weight for a period of 36 weeks. Growth was significantly depressed at the two highest levels (158 and 500 mg/kg). Also, the coagulation and prothrombin times of the blood were extended. At both levels, liver cholesterol was elevated, and fatty changes were seen in the liver at the highest level. Increased mortality occurred in the males at the highest level.

Oral data of this sort are difficult to extrapolate to industrial uses. However, the data do indicate that this material is not highly toxic. There are no reported cases of ill effects from its use in industry.

12. *N-Cyclohexyl-N'-phenyl-p-phenylenediamine (Flexzone 6H)*[2].—Experimental toxicology carried out by Uniroyal, Inc.[10] shows an acute oral LD_{50} for rats of >2000 mg/kg. This Company also reports that it is a skin sensitizer, particularly to those individuals who are already sensitized to any phenylenediamine.

Skin contact should be avoided.

13. *1,4'-Diaminodiphenylmethane (Tonox)*[2].—The manufacturer of this product, Uniroyal, Inc., has performed 2-yr feeding studies with rats at a dietary level of 0.1%[10]. Specific details of the study are not available, except that there was no evidence of any carcinogenicity. The primary target, so far as toxic effects are concerned, seems to be the liver. Care should be taken in handling this material in industrial uses to avoid inhalation of the dust or, if at elevated temperatures, of the vapors.

14. *2,5-Di-tert-amylhydroquinone (Santovar A)*[2].—Experimental animal studies, using both rats and rabbits, show that the oral LD_{50} for both species is >2000 mg/kg. Rats have been fed 35 mg per day for 175 days (1800 ppm of the diet) with no adverse effects[5].

The manufacturer of the product, The Monsanto Company, reports it has had no problem with customers using this product over many years[5].

15. *N,N'-Di-β-naphthyl-p-phenylenediamine (Agerite White)*.—Mallette and von Haam report a low degree of acute oral toxicity in rats, 4.5 g/kg as an LD_{50}. These same authors reported a slightly irritating and a slightly sensitizing effect when applied to the skin of humans[14]. Other dermatology studies carried out by the repeat insult technique on humans have shown it to be a primary irritant, but not a sensitizer or a depigmenting agent[15].

This antioxidant has been used for many years in the rubber industry with no significant physiological problems. Because of its skin irritant effect, skin contact should be avoided.

16. *2, 6-Di-tert-butyl-α-dimethylamino-p-cresol (Antioxidant 703)*.—The only available toxicology on this compound is a reported oral LD_{50} (presumably

for rats) of 1030 mg/kg[16]. This value would indicate that it is not severely toxic. There are no known reported cases of ill effects in its use.

17. *2, 6-Di-tert-butyl-p-cresol (butylated hydroxytoluene, BHT)*[2].—This is one of the most widely used food antioxidants; its use in the rubber industry is limited. It has been studied extensively with respect to toxicology. An oral LD_{50} for the rat is reported to be 1.7–1.97 g/kg by Deichmann and coworkers[17]. Two-year feeding studies with rats, by these same investigators, showed no significant findings at daily dietary levels of 0.2, 0.5, or 0.8%

Mallette and von Haam[14] found a considerably higher LD_{50} for rats (8 g/kg) and "moderate" to "slight" skin irritant effects to humans.

This compound, while of a low order of toxicity orally, may be somewhat irritating to the skin with prolonged contact. Handling procedures should, therefore, be designed to prevent this.

18. *N,N'-Di-sec-butyl-p-phenylenediamine (Tenamene 2)*.—The manufacturer of the product, Tennessee Eastman Company, reports an oral LD_{50} for rats of 200–400 mg/kg and a percutaneous LD_{50} for guinea pigs of 5–10 ml/kg[9]. Moderately severe eye damage also occurred with direct instillation into the rabbit's eye. It is strongly irritating to the skin and is a sensitizer. Proper handling controls should be established to prevent skin and eye contact wherever it is used.

19. *1,2-Dihydro-2,2,4-trimethyl-6-ethoxyquinoline (Santoflex AW)*[2].—The acute oral LD_{50} for rats has been found to be 800 mg/kg. Rats have been fed daily dietary levels containing 0.2% and 0.4% for 200 days; all pathology was negative. Rabbits have been exposed for 20 h, over a 3 day period, to vapors generated by dropping the product onto a metal surface heated to 325° F. Only respiratory discomfort and mild lacrymation resulted. Twenty workers have participated in a use test whereby rubber gloves containing this antioxidant were worn for five days a week for six weeks. No skin irritation resulted[5].

This antioxidant has been used for many years in the rubber industry, and the history of this use has been favorable.

20. *1,2-Dihydro-2,2,4-trimethyl-6-dodecylquinoline (Santoflex DD)*[2].—An acute oral minimal lethal dose for rats has been found to be in excess of 40 g/kg, and an acute skin minimal lethal dose for rabbits to be >10 g/kg. Mild skin and eye irritation occurred to the rabbits when treated with the compound[5]. There have been no reported ill effects from the use of this product. Based upon animal data, it is prudent to keep it off the skin and to prevent contact with the eyes.

21. *1,2-Dihydro-2,2,4-trimethylquinoline, polymerized (Agerite Resin D, Flectol H)*.—The lethal single dose to rabbits has been found to be about 2 g/kg. Application to the skin of rabbits produced no signs of irritation[15]. Hodge and coworkers[18] have fed daily dietary levels of 0.01, 0.1, and 1.5% to rats for 2 yr and have observed the formation of tumors in some of the animals. Similar studies with dogs for a 1-year period at daily dietary levels of 0.008, 0.03, and 0.15% produced no tumors.

This antioxidant has been used for a great many years in the rubber industry with no reported cases of ill effects.

22. *Diphenylamine-acetone resin (Aminox, Agerite Superflex, BLE, BLE-25)*[2].—This resinous product has no specific chemical structure. No experimental toxicology has been reported; however, the experience during more than 30 years' use has been entirely favorable.

23. *Diphenylamine-acetone-formaldehyde resin (BX-1-G)*[2].—This resin has

no specific chemical structure; there are no reported experimental toxicology data. However, it has been used in the rubber industry for many years and the history of this use is quite favorable.

24. *N,N'-Diphenylenediamine* (*Agerite DPPD, JZF*)[2].—This old antioxidant has been studied quite extensively with respect to toxicology. In the early 1950's, it was found to have distinct advantages when used in poultry feed to prevent the occurrence of the serious poultry disease, encephalomalasia, and was used on a commercial basis for this purpose. However, observations by Oser in 1956[19], showing an adverse effect upon the parturition of pregnant rats (a lengthening of the gestation period with subsequent increased mortailty to both the mother and the litter), required the removal of DPPD from the market for this purpose. This work has been confirmed in unpublished studies by The B. F. Goodrich Company[15].

Except for the peculiar effect on parturition of rats, DPPD has a low degree of toxicity. When fed as a 20% aqueous suspension to rats, the minimal lethal single dose is in excess of 10 g/kg. Furthermore, when fed at a daily dosage of 1.4 g/kg to rabbits over a 5–6 week period, no signs of illness or interference with normal growth rate was observed[15]. One year feeding studies in Rhesus monkeys at levels of 1, 20, and 400 mg/kg per day showed no toxic effects and no significant histological findings[20].

Patch tests conducted on 91 humans, using commercial DPPD, showed no positive effects when tested with a 48 h contact. No sensitivity reaction were found when tested on the same personnel after a two week waiting period[15].

Use of this antioxidant in the rubber industry for many years has demonstrated its freedom from any significant handling problem. No special precautions are needed.

25. *Hydroquinone* (*Tecquinol*).—Acutely, hydroquinone is somewhat more toxic than phenol. The approximate lethal oral dose of this compound in aqueous solutions has been reported to be 0.2 g/kg for the rabbit[21] and 0.08 g/kg for the cat[22]. However, experimental studies in animals and men have demonstrated a relatively low degree of chronic toxicity. The compound is capable of causing skin irritation from prolonged repeated contact[6].

Sterner and associates have reported on the major hazard arising from daily exposure to hydroquinone, *i.e.*, the development of brownish discoloration of eye tissue (cornea and conjunctiva)[23]. These eye changes may lead to decreased visual acuity. Also, direct eye contact may result in severe eye irritation. Systemic effects from industrial exposure have not been observed.

Precautions should be taken in the handling of hydroquinone to prevent its entrance into the eye. If this should occur accidentally, immediate washing for a minimum of 15 min with water is necessary, and this followed by prompt referral to a physician. A TLV of 2 mg/m^3 has been established[24].

26. *p-Isopropoxydiphenylamine* (*Agerite ISO*)[2].—The minimal lethal oral dose for rats is <10 g/kg and for rabbits <7 g/kg. This compound has been administered orally to rabbits at a dose of 1.4 g/kg, 5 days per week, over a 5–6 week period[15]. No toxic effects occurred, although some weight loss resulted in the first 3 weeks of the experiment. This was believed to be caused by the animals' rejection of food at this high dosage level. The compound has been maintained in contact with skin of rabbits at a level of 1.5 g/kg for 4 h per day, 5 days per week, over a 5–6 week period. No signs of toxicity occurred, and there were no signs of skin irritation[15].

Routine 48 patch tests have been conducted on 91 adults with a challenge

application made at the end of a 2 week waiting period. These studies showed the compound to be neither a primary irritant nor a sensitizer[15].

This compound has been used for many years in the rubber industry with completely favorable results. No special handling precautions are needed.

27. *N-Isopropyl-N'-phenyl-p-phenylenediamine (Flexzone 3C, Santoflex 36)*[2]. —An acute oral LD_{50} for rats of 720 mg/kg is reported. Human patch tests performed with the compound in concentrated form, as well as rubber containing the compound as an antioxidant, show it to be a skin sensitizer[10].

The Monsanto Company has determined an acute oral LD_{50} for rats, when administered as a 10% suspension in methyl cellulose, to be 1620 mg/kg. The acute minimal lethal dose by skin absorption, when administered as a 50% suspension in methyl cellulose, for rabbits is >7500 mg/kg. This compound proved to be mildy irritating to the skin of rabbits and slightly irritating to the eyes of rabbits[5].

Appropriate handling precausions to prevent skin contact should be observed in any industrial uses.

28. *2,2'-Methylene-bis(4-ethyl-6-tert-butylphenol) (Antioxidant 425)*[2].—This compound is practically non-toxic from an acute oral standpoint. An LD_{50} for rats, when administered as an aqueous suspension, is in excess of 15 gm/kg[4]. Single doses of 1, 4, and 8 g/kg have been applied to the skin of rabbits and kept in contact with it for 18 h. No signs of systemic toxicity occurred, and there was no evidence of skin irritation beyond a mild redness at the two highest dosage levels. When three milligrams of the dry powder were placed in the eyes of rabbits, only a mild inflammatory reaction occurred. Rats have been fed daily dietary levels of 100, 1000, and 10,000 ppm over a 5 week period. No significant signs of toxicity were found, although the rats receiving the highest level showed marked retardation of growth[4].

This antioxidant has been used in the rubber industry for a number of years with no reported instances of ill effects.

29. *2,2'-Methylene-bis(4-methyl-6-nonylphenol) (Nauga White)*[2].—An acute oral LD_{50} for rats of 32.7 g/kg has been reported. The compound has been fed at a level of 5% of the daily diet to rats for 90 days with no signs of toxicity, either grossly or at necropsy. Studies with rabbits indicate that it is not a primary irritant or skin sensitizer[10]. It has been used without any known problems in the rubber industry for a number of years.

30. *2,2'-Methylene-bis(4-methyl-6-tert-butylphenol) (Antioxidant 2246)*[2].— Considerable work has been devoted to a study of the physiological effects of this antioxidant. It has a low level of acute oral toxicity, being above 5 g/kg, when administered as an aqueous suspension to mice. Repeat doses to the skin of rabbits of 0.4 g/kg as a 10% solution in Wesson oil and held in contact with the skin for approximately 18 hours on alternate days for a total of 6 applications showed no signs of systemic toxicity[4]; however, there were severe degrees of skin irritation. A 1% solution in oil, and as an oil-water emulsion, produced no appreciable degree of irritation in the eyes of rabbits. Oral feedings have been made to rats at daily dietary levels of 200, 1000, and 5000 ppm for a 13 week period. No signs of toxicity occurred, except some retardation in the growth of male rats at the highest feeding level[4].

This antioxidant has a low degree of toxicity and requires no special handling procedures in industrial use.

31. *Hydroquinone monobenzyl ether (Agerite Alba)*[2].—This old rubber antioxidant is a well-recognized depigmenting agent. Its ability to produce leuko-

derma was first established by McNally[25] and has since been well substantiated by Klander[26] and other investigators. Blank and Miller[27] and Gaul[28] have also found it to be irritating to the skin of a substantial number of people, either as the virgin compound or as an ingredient of rubber stocks.

Denton and coworkers[29] have fed this compound to guinea pigs at a daily dose of 160 mg/kg for a 2 month period. Depigmentation of the hair occurred, but there were no other signs of toxicity. Peck and Sobotka[30] have fed it to guinea pigs in an approximate amount of 12 g over a 5 month period. No depigmentation of the skin or hair occurred, and there were no signs of toxicity. Lerner and Fitzpatrick[31] found no toxic changes in mice which were injected intraperitoneally with 600 mg/kg per day for a 3 week period. Kelly and coworkers[32] have found that cancer patients tolerated oral doses of up to 10 g per day without signs of toxicity.

Careful use of this compound is necessary in order to avoid skin contact.

32. *Monooctyl and dioctyldiphenylamine (Agerite Stalite, Agerite Stalite S, Octamine).*—Agerite Stalite has been fed to rats at three levels in their daily diet: 2500, 5000, and 10,000 ppm over a 64 week period. No increased incidence of mortality was found at any of the feeding levels. Some mild effects on the liver were observed at necropsy[15].

Human patch tests performed with Agerite Stalite using the repeat insult technique show that it is neither a primary irritant, a sensitizer, nor a depigmenting agent[15]. The single minimal lethal oral dose for rabbits is approximately 15 ml/kg[15].

These antioxidants have been used widely for a number of years in the rubber industry with no reported occurrences of adverse effects.

33. *Nickel dibutyldithiocarbamate (NBC).*—The approximate lethal oral dose for rats is 17 g/kg. When applied to the skin of guinea pigs as a 10% solution in an acetone-dioxane mixture, no skin irritation occurred. A 20% solution, similarly applied, produced only mild erythema. There were no signs of sensitivity.

Moderately careful handling should be exercised in using this compound, inasmuch as exposure to nickel compounds carries some potential risk.

34. *Phenyl-α-naphthylamine (Neozone A)*[2].—Long-term feeding studies have been conducted using 3 dogs, with a daily administration of 290 mg 5 days per week for 36 to 42 months. No signs of toxicity were found, including the absence of bladder tumors[33].

Application of an aqueous paste to the skin of each of 199 human volunteers did not cause skin irritation or sensitization[33].

Recent data developed by highly sensitive analytical procedures have shown the presence of β-naphthylamine up to 30 ppm in phenyl-α-naphthylamine[34]. This is believed to be toxicologically insignificant, inasmuch as phenyl-α-naphthylamine has perhaps always contained β-naphthylamine of about this same level and no adverse effects have been seen in either animals or humans with phenyl-α-naphthylamine over many years of use.

35. *Phenyl-β-naphthylamine (Agerite Powder, Neozone D)*[2].—Rats have been fed dietary levels up to 1% of their daily diet for 71 weeks with no signs of carcinogenicity; however, some kidney damage was found. Three dogs have been fed 540 mg, five days per week for 50–54 months, and one dog 100 mg/kg per day for 45 months. No signs of bladder tumors or other toxicity were found[33].

The similarity in name between phenyl-β-naphthylamine and the recog-

nized human carcinogen, β-naphthylamine has been the cause of much concern with respect to the carcinogenicity of phenyl-β-naphthylamine over many years. This is one of the oldest antioxidants used in the rubber industry, and the experience in this use has been entirely favorable. Both Williams[35] and Scott[36] have cited the absence of bladder tumors in producers and users of phenyl-β-naphthylamine.

Recent data acquired through the use of highly sensitive analytical procedures have shown the presence of β-naphthylamine in commercial grades of phenyl-β-naphthylamine up to 50 ppm[34]. This is believed to have no toxicological significance, inasmuch as the commercial grade of phenyl-β-naphthylamine has probably always contained levels of this much β-naphthylamine, but its use has not been associated in any way with the production of bladder tumors.

36. *Phenyl-β-naphthylamine-acetone resin* (*Betanox Special*)[2].—There is no experimental toxicology reported. Its use in the rubber industry has been very favorable.

37. *Polyalkylpolyphenol* (*Agerite Superlite*).—Oral feeding studies[15] have been conducted with rats over a 62 week period using three dietary levels of 2500, 5000, and 7500 ppm. The highest level produced some increased mortality. The principal sites of toxic effects were the kidney and liver. These feeding levels, of course, are relatively high for prolonged feeding, and even though effects were observed, the compound is not regarded as very toxic. Its use in the rubber industry, over many years, has been entirely favorable.

38. *Styrenated phenols* (*Wingstay S, Agerite Spar*)[2].—The Goodyear Tire and Rubber Company has performed chronic feeding studies on Wingstay S. Five graded doses have been fed to rats at levels ranging from 5 to 500 mg/kg for a 36 week period. Retardation of growth was found at the two highest levels, 158 and 500 mg/kg. At the end of 12 weeks, no other signs of toxicity were seen[13].

39. *Butylated-styrenated phenol* (*Wingstay V*).—Two-year feeding studies with Wingstay V on rats and dogs, at levels up to 158 mg/kg per day, produced no evidence of toxicity, except moderate depression of food intake and body weight in the case of rats at the highest dosage level. At 50 mg/kg per day, all responses were normal in both species[13].

40. *N-Stearoyl-p-aminophenol* (*Suconox 18*).—The only reported experimental toxicology indicates an oral LD_{50} for rats of <11 g/kg[37].

There have been no reported ill effects from use of this compound in the rubber industry.

41. *4,4′-Thio-bis(di-sec-amylphenol)* (*Santowhite L*).—The acute oral minimal lethal dose for rats, administered in undiluted form, is >20 g/kg, while the acute minimal lethal dose by percutaneous absorption for rabbits, administered in undiluted form, is >10 g/kg. The compound is non-irritating to the skin of rabbits. It produces slight irritation when administered undiluted into the eyes of rabbits[5].

There are no reported ill effects associated with industrial use of this antioxidant.

42. *4,4′-Thio-bis(6-tert-butyl-m-cresol)* (*Santowhite Crystals*)[2].—The Monsanto Company reports an acute oral LD_{50} for rats, when fed as a 50% suspension in olive oil, of 2345 mg/kg, and for rabbits approximately 3200 mg/kg. Rats have been fed dietary levels of 0.005 and 0.05% for 3 months with no signs of toxicity except a retardation of growth at the 0.05% level[5]. The

Monsanto Company has conducted human patch tests using 200 human volunteers and rubber patches containing Santowhite Crystals as the antioxidant. The results have been favorable, indicating that it is neither a primary irritant nor sensitizer[5].

43. *4,4'-Thio-bis(6-tert-butyl-o-cresol)* (*Ethyl Antioxidant 736*).—This sterically hindered phenolic antioxidant has a reported acute oral LD_{50} of 6340 mg/kg when administered as a 20% solution in peanut oil[38] (presumably to rats). This is a relatively low level of toxicity. No special handling procedures are recommended by the manufacturer.

44. *N-Phenyl-N'-(p-toluenesulfonyl)-p-phenylenediamine* (*Aranox*)[2].—There is no reported experimental toxicology for this antioxidant. It has over 30 years' use in the rubber industry with no reported cases of any problems.

45. *Tri(mixed mono and dinonylphenyl)phosphite* (*Polygard*)[2].—The acute oral toxicity for rats shows an LD_{50} of 19.5 g/kg. Two-year feeding studies were performed with rats and dogs at dietary levels up to 1 wt% of the food[10]; slight toxic effects were seen at the highest level. Repeated application of the undiluted compound to the skin of rabbits has produced definite but transient skin irritation but no evidence of systemic toxicity[10].

Based upon animal experimentation, there appears to be some risk from skin irritation in industrial use of this compound. However, the history of its use over a number of years has been favorable.

46. *1,3,5-Trimethyl-2,4,6-tris(3,5-di-tert-butyl-4-hydroxybenzyl) benzene* (*Antioxidant 330*).—This compound has a very low oral toxicity, with a reported acute LD_{50} value of 15 g/kg (presumably to rats). Ninety-day feeding studies to rats at a dietary level of 3.16% produced no significant effects[39]. It is permitted up to 0.5 wt % in polymers by the U. S. Food and Drug Administration for food contact applications[40].

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