STUDIES ON THE TOXICITY AND SKIN EFFECTS OF COMPOUNDS USED IN THE RUBBER AND PLASTICS INDUSTRIES

II. Plasticizers

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INDUSTRIAL ASPECTS

PLASTICIZERS are frequently added to synthetic resins to increase their flexibility and extensibility. According to Powers,[1] they are not so much desirable as necessary. Plasticizers serve two important functions[2]: They reduce the viscosity of resins at processing temperatures, and they soften the resin at normal temperatures, yielding flexible materials. Resins high in vinyl chloride content can be calendered or molded only with difficulty, and the addition of a plasticizer greatly improves the calendering process.

Since plasticized vinyl resins are used in hundreds of articles of commerce, the choice of the plasticizer depends upon the ultimate use of the compound. Most of the plasticizers, especially those used for vinyl resins, are compounds with a high boiling point, usually above 200 C. For this reason industrial exposure to the vapors of these compounds is observed only near the areas of vaporization. In the plants surveyed, the plasticizers are added to the resins in the semidry state and mixed in large or small blenders, together with the coloring agents, stabilizers, and other ingredients. The mixture is then charged into a Banbury mixer, in which the temperatures may exceed 200 C., resulting in some vaporization of the plasticizer. However, Banbury mixers are usually enclosed and ventilated, and consequently normally no undue exposure to the vapors can occur. From the Banbury mixer the hot mass is dropped onto a mill, from which it may either be sheeted off for future use or may be fed directly into the calender. At the mill or the calender, large amounts of vaporized plasticizer may escape. For this reason it is advisable to hood and exhaust these machines. Condensed plasticizers may reduce the efficiency of the exhaust system, so that periodic cleaning of the ducts and fans may become necessary. During the periods of reduced efficiency of the exhaust system, resulting escape of plasticizer vapors, complaints of irritation of the eyes and respiratory tract with occasional reports of headache and nausea, have been received.

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1. Powers, P. A.: Synthetic Resins and Rubbers, New York, John Wiley & Sons, Inc., 1943.

2. Reed, M. C.: Survey of Plasticizers for Vinyl Resins, J. Polymer Sc. 2:115, 1947.

REVIEW OF THE TOXICOLOGICAL LITERATURE

Few data on the toxicity of plasticizers or on their hazard to health are available. The gums, oils, and resinous materials, of which there are literally hundreds in use as softeners, are almost universally considered nontoxic with the exception of certain irritating tars and pitches.[3] Orthotricresyl phosphate presents a definite industrial health hazard. In experimental animals it produces toxic hemorrhages in the lungs, liver, kidneys, and spleen and degeneration of the motor nerve cells. The phthalic acid derivatives (dibutyl and diethyl phthalate) are not seriously toxic but may produce skin affections and an anemic condition in animals. Vapors of 2-ethylhexyl phthalate have produced delayed death in rats with liver and kidney injury.[4] Diphenylguanidine was reported as nontoxic to animals by Davis,[5] who concluded that the conjunctivitis, bronchitis, and dermatitis encountered in workers were due to impurities rather than to the compound itself. Of the solvent plasticizers used in the synthetic rubber industry, acetone, amyl acetate, benzene, and benzine have been thoroughly investigated, and it has been found that they may exert toxic influences upon the lung, liver, kidney, or blood-forming organs. Benzine also has an injurious effect upon the central nervous system. Carbitol® (diethylene glycol monoethyl ether) is only slightly toxic unless contaminated with diethylene glycol.[6] The latter causes kidney injuries leading to anuria and uremia.[7] Diethylene dioxide ("dioxane"), is a plasticizer for synthetic rubber. It is a mild pulmonary irritant, and prolonged exposure to it may lead to severe injury of liver and kidney.[8] The various forms of cellosolve® (methyl cellosolve,® methyl and diethyl, butyl and dibutyl cellosolve®) are all ethers of ethylene glycol and are widely used as solvent plasticizers for acetyl cellulose, nitrocellulose, and soluble resins. They have slight irritating effects on the mucous membranes and toxic effects on the kidneys.

Glycerin is practically nontoxic and causes symptoms only when administered in high doses. Lactate (ethyl and butyl lactate) in high doses causes death of experimental animals from respiratory paralysis.[7] Carbon disulfide and the chlorinated hydrocarbons are strong narcotics in high concentrations and may act as local lung irritants.[9] Repeated exposure produces nephritis with albuminuria and fatty degeneration of the liver. The toxicity of the chlorinated hydrocarbons is variable, and industrial hazard depends on the volatility as well as on the toxicity of

3. Hamilton, A.: Industrial Poisons in the United States, New York, The Macmillan Company, 1925.

4. Shaffer, C. B.; Carpenter, C. P., and Smyth, H. F., Jr.: Acute and Subacute Toxicity of Di(2-Ethylhexyl) Phthalate with Notes upon Its Metabolism, J. Indust. Hyg. & Toxicol. 27:130, 1945.

5. Davis, P. A.: Toxic Substances in the Rubber Industry: XVI. Guanidine Compounds, Rubber Age 28:143, 1930.

6. Hanzlik, P. J.; Lawrence, W. S.; Fellows, J. K.; Induana, F. P., and Laqueur, G. L.: Epidermal Application of Diethylene Glycol Monoethyl Ether (Carbitol) and Some Other Glycols: Absorption, Toxicity and Visceral Damage, J. Indust. Hyg. & Toxicol. 29:325, 1947.

7. Lehmann, K. B., and Flury, F.: Toxicology and Hygiene of Industrial Solvents, Baltimore, Williams & Wilkins Company, 1943.

8. Barber, H.: Hemorrhagic Nephritis and Necrosis of the Liver from Dioxane Poisoning, Guy's Hosp. Rep. 84:267, 1934.

9. Von Oettingen, W. F.: The Halogenated Hydrocarbons: Their Toxicity and Potential Dangers, J. Indust. Hyg. & Toxicol. 19:349, 1937.

the compounds. The cyclic hydrocarbons occupy a middle position with regard to toxicity. Cyclohexyl acetate is more toxic but less volatile than amyl acetate and produces hemorrhagic edema of the lungs and paralysis of the central nervous system. Unsaturated hydrocarbons are usually more toxic than the corresponding saturated compounds.[7]

This brief survey presents the laboratory evidence on the chemical groups to which the majority of plasticizers belong. However, the constant introduction of new compounds demands continual investigation, and each new compound should be properly studied as to its toxicological properties in order to estimate its industrial health hazard.

METHODS AND MATERIAL

Twenty-five compounds which are used at present as plasticizers of synthetic resins have been investigated. They are listed according to their chemical classification in Table 1.[8] The last group includes compounds whose chemical composition is a proprietary secret and have therefore been listed under their trade name with the name of the manufacturer in parenthesis.[10]

TABLE 1.—*Compounds Used as Plasticizers*

1. Adipic acid derivatives
   Di-2-ethylhexyl adipate ("adipol 2EH")
2. Azelaic acid derivatives
   Cyclohexyl azelate
   Dibutyl cellosolve® azelate
   2-ethylhexyl azelate
   Methyl isobutyl carbinol azelate
   Pentanol azelate
3. Capric acid derivatives
   Diethyleneglycol dicaprate
4. Carbonic acid derivatives
   Dibutoxyethyl diglycol carbonate
5. Nitrile derivatives
   Octadecene nitrile
6. Phthalic acid derivatives
   Dibutoxyethyl phthalate ("kronisol")
   Dicapryl phthalate
   Dioctyl phthalate
   Butylbenzyl phthalate ("santicizer 160")
7. Ricinoleic acid derivatives
   Methylacetyl ricinoleate ("Baker's P4")
8. Sebacic acid derivatives
   Dioctyl sebacate
   Dibutyl sebacate
9. Trade-name plasticizers
   "Flexol 8N8" (Carbide & Carbon)
   "Plasticizer 50 B" (Barrett)
   "Plasticizer Ellicott H"
   "Plasticizer SC" (Drew)
   "Paraplex G-25" (Rohm & Haas)
   "Paraplex G-40" (Rohm & Haas)
   "Santicizer 140" (Monsanto)
   "Santicizer 141" (Monsanto)
   "Plastolein X-55" (Emery)

For the determination of toxicity the same methods were used as given in the report on the toxicity of accelerators, activators, and antioxidants.[10] Since most of the plasticizers are insoluble in water, mineral oil or propylene glycol was used as diluent. The criteria for the determination of toxic effects were the minimal lethal doses, the clinical symptoms, and the histological changes as revealed by postmortem examination. For the determination of the $L.D._{100}$, Smyth's range-finding test was used as a first step and was combined in a second series of experiments with the logarithmic toxicity scale of Deichmann. In the average experiment 16 to 18 animals sufficed for obtaining a clear-cut result. The skin effects of the plasticizers were determined by application to the skin of experimental animals and human volunteers. Two

10. Because of the proprietary nature of many of these compounds exact information as to their composition cannot be obtained. The following information may not be entirely accurate:

"Flexol 8N8" = N,N-di-beta-(2-ethylhexyl)ethyl 2-ethylhexamide
"Plasticizer" 50B" = butylcyclohexyl phthalate
"Plasticizer SC" = triethylene glycol dicaprylate
"Paraplex G-25" = probably condensation products of sebacic
"Paraplex G-40" = acid with glycols and/or glycerin
"Santicizer 140" = monotolyldiphenyl phosphate
"Santicizer 141" = monooctyldiphenyl phosphate (?)
"Plastolein X-55" = diethylene glycol di-pelargonate

to four white rabbits were used for preliminary testing of skin irritability and sensitization, and each compound was then tested on 15 to 30 human subjects. The patch test was used and the reaction classified as slight, moderate, or severe. Sensitization tests were performed two weeks after the primary irritation test.[11]

RESULTS

Toxicity Investigations.—Table 2 lists the compounds which have been found nontoxic or practically nontoxic. The animals supported intraperitoneal injection of 6 gm. or more per kilogram of body weight without showing any immediate or delayed effects. All animals were subjected to autopsy after one month of observation. Careful histological examination of all organs failed to show any evidence of pathologic change. The injected material could often be found remaining in the peritoneal cavity, surrounded by necrotic formed adhesions and fibrous tissue. Microscopically, foreign body granulomas could be observed and some of the material could be followed in the endothelial cells of the liver and spleen.

Five of the plasticizers examined showed a moderately toxic effect in laboratory animals. They were dioctyl phthalate, butylbenzyl phthalate, "santicizer 140,"

TABLE 2.—*Nontoxic Plasticizers*

Di-2-ethylhexyl adipate	Dicapryl phthalate
Cyclohexyl azelate	Methylacetyl ricinoleate
Dibutyl cellosolve azelate	Dioctyl sebacate
2-ethylhexyl azelate	Dibutyl sebacate
Methyl isobutyl carbinol azelate	"Plasticizer 50 B" (Barrett)
Pentanol azelate	"Plasticizer Ellicott H"
Diethylene glycol dicaprate	"Plasticizer SC" (Drew)
Dibutoxyethyl diglycol carbonate	"Paraplex G-25" (Rohm & Haas)
Octadecene nitrile	"Paraplex G-40" (Rohm & Haas)
Dibutoxyethyl phthalate	"Plastolein X-55" (Emery)

"santicizer 141," and "flexol 8N8." Intraperitoneal injection of dioctyl phthalate proved fatal in doses higher than 2 gm. per kilogram of body weight. Lower doses produced weight loss, leucocytosis, severe anemia, and hematuria, from which the animals recovered after one to two months. No delayed effect or permanent injury was noted in the surviving animals.

Butylbenzyl phthalate killed rats after intraperitoneal administration of doses higher than 1.8 gm. per kilogram of body weight. Oral administration of more than 4 gm. per kilogram of body weight proved equally fatal. The animals died after four to eight days, showing weight loss, apathy, and leucocytosis. The histological examination of the organs revealed toxic splenitis and degenerative lesions of the central nervous system with congestive encephalopathy, myelin degeneration, and glial proliferation.

"Santicizer 140" proved fatal in intraperitoneal doses of higher than 1 gm. per kilogram of body weight. Oral doses up to 4 gm. were supported. Toxic animals became lethargic on the second or third day, and a profuse diarrhea developed. They died with symptoms of paralysis. Autopsy showed a generalized capillary paralysis with severe edema and numerous small hemorrhages in the brain.

11. Mallette, F. S., and Von Haam, E.: Studies on the Toxicity and Skin Effects of Compounds Used in the Rubber and Plastics Industries: I. Accelerators, Activators, and Antioxidants, A. M. A. Arch. Indust. Hyg. 5:311, 1952.

"Santicizer 141" killed animals after intraperitoneal administration of doses higher than 2.4 gm., but oral administration of 4 gm. per kilogram of body weight was tolerated. With the intraperitoneal administration, the animals became paralyzed and lethargic. Recovery from nonfatal lesions was delayed. The histopathological examination demonstrated a severe acute hemorrhagic encephalopathy with cerebral edema, ganglion cell degeneration, and small hemorrhages. As delayed effects, focal gliosis and persistent foci of myelin degeneration could be observed.

TABLE 3.—*Determination of Skin Effects*

	Animal Tests (Conc. 100%)		Human Tests						
Name of Compound	Irritative Effect	Sensitizing Effect	Concentration, %	Negative Reaction, %	Light Reaction, %	Severe Reaction	Sensitized, %	Irritative Effect	Sensitizing Effect
Adipic acid derivatives									
Di-2-ethylhexyl adipate	0	0	100	100	0	0	0	0	0
Azelaic acid derivatives									
Cyclohexyl azelate	0	0	100	74	26	0	3	Moderate	Slight
Dibutyl cellosolve® azelate	0	+	100	47	53	0	0	Moderate	0
2-ethylhexyl azelate	0	+	100	85	15	0	0	Slight	0
Methyl isobutyl carbinol® azelate	0	0	100	30	70	0	7	Moderate	..
Pentasol azelate	0	+	100	60	40	0	0	Moderate	0
Capric acid derivatives									
Diethylene glycol dicaprate	++	0	100	97	3	0	10	Slight	Moderate
Carbonic acid derivatives									
Dibutoxyethyl diglycol carbonate	0	0	100	0	0	0	0	0	0
Nitrile derivatives									
Octadecane nitrile	0	+	100	87	13	0	0	Slight	0
Phthalic acid derivatives									
Dibutoxyethyl phthalate	0	0	100	100	0	0	0	0	0
Dinpryl phthalate	++	0	10	90	10	0	0	Moderate	0
Dioctyl phthalate	++	0	10	87	13	0	3	Moderate	Slight
Butylbenzyl phthalate	++	+	10	88	12	0	0	Moderate	0
Ricinoleic acid derivatives									
Methylacetyl ricinoleate	++	0	100	90	10	0	12	Slight	Moderate
Sebacic acid derivatives									
Dioctyl sebacate	0	0	100	100	0	0	0	0	0
Dibutyl sebacate	0	0	100	100	0	0	0	0	0
Trade-name plasticizers									
"Flexol 8N8"	0	+	25	55	40	5	3	Severe	Slight
"Plasticizer 50 B"	++	+	10	85	15	0	0	Moderate	0
"Plasticizer Ellicott H"	0	0	100	74	26	0	0	Moderate	0
"Plasticizer 8C"	0	0	100	60	40	0	0	Moderate	0
"Paraplex G-25"	++	0	25	32	68	10	16	Severe	Moderate
"Paraplex G-40"	0	0	25	48	52	0	13	Severe	Moderate
"Santicizer 140"	+	0	10	90	10	0	0	Moderate	0
"Santicizer 141"	+++	0	5	90	10	0	10	Moderate	Moderate
"Plastolein X-55"	0	0	100	93	7	0	0	Slight	0

Large fatal doses also proved a powerful hemolytic agent with marked vascular hemolysis, hemoglobinuria, and hemosiderosis of the spleen.

"Flexol 8N8" proved fatal in doses higher than 4.0 gm. per kilogram of body weight. The animals developed convulsions followed by paralysis. The histological examination of the brain gave the picture of toxic hemorrhagic encephalopathy with edema, swelling of ganglion cells, and small hemorrhages.

Skin Effects.—The results of the studies on the effects of the plasticizers on the skin are shown in Table 3.

Preliminary experiments on animals always preceded the application of the compound to human subjects. Sensitizing effects were studied after a two-week

interval had elapsed. From the table it can be seen that only five compounds proved neither irritating nor sensitizing. Six compounds had some sensitizing effect on animals but were innocuous in the human investigations. All compounds which produced primary irritation on the animal skin also proved irritating to the human skin. Twenty compounds produced a definite reaction on the human skin. Five produced a reaction in approximately 10% of the persons tested, and six produced a reaction in more than 30% of those tested. "Paraplex G-25" and "flexol 8N8" produced reactions which must be regarded as uncommonly severe. Nine compounds produced some sensitizing effect on the human skin, with "paraplex G-25" and "paraplex G-40" the severest sensitizers. The following plasticizers proved entirely innocuous in the concentrations tested: di-2-ethylhexyl adipate, dibutoxyethyl diglycol carbonate, dibutoxyethyl phthalate, dioctyl sebacate, and dibutyl sebacate.

SUMMARY

The toxicity and skin effects of 25 plasticizers were tested by standardized methods. Five of the plasticizers proved moderately toxic in doses from 0.6 to 2.4 gm. per kilogram of body weight. The toxic reaction was displayed by the erythrocytes, the blood capillaries, and the central nervous system. Seventeen plasticizers proved to be slight or moderate skin irritants, three proved to be severe skin irritants, and five proved to be moderate sensitizers. Five plasticizers showed no irritating or sensitizing effect, and the lack of toxic properties recommends them as the most innocuous compounds tested in this series.