OCCUPATIONAL DISEASES IN SYNTHETIC RESIN AND FIBRE INDUSTRIES

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The prosperity of the synthetic resin and fibre industries in Japan today is accompanied by a rise of incidence of the occupational poisoning and skin disease. In this paper are sketched occupational diseases caused by raw materials, intermediate products(monomers and polymers), solvents and stabilizers of the synthetic resin and fibre industries, and also is informed the incidence of these diseases, summarizing the latest literatures.

INTRODUCTION

If the existing concept that industrial property brings unbalance of supply and demands to increase the incidence of occupational diseases, the current rapid development in synthetic resin and fibre industries will be a great concern to all of us. In fact, many companies have consulted our office about this concern, and there is also an increase in the number of papers published abroad on this subject.

In view of this situation, therefore, occupational diseases caused by raw materials, intermediate products, solvents and stabilizers used in synthetic resin and fibre industries are sketched and reviewed in this communication.

1. PRODUCTION PROCESSES FOR SYNTHETIC RESINS AND FIBRES

Manufacturing processes for synthetic resins and fibres currently in use or those which have been proposed but have never been used are summarized in the tables[1](Tables 1, 2 I, II).

Occupational diseases can be caused by raw materials, monomers, polymers, solvents and additives, and in this review, they will be discussed in this order.

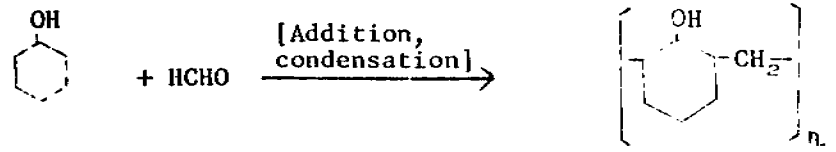
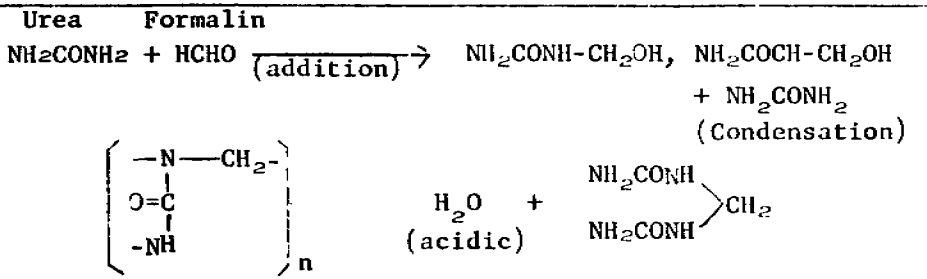
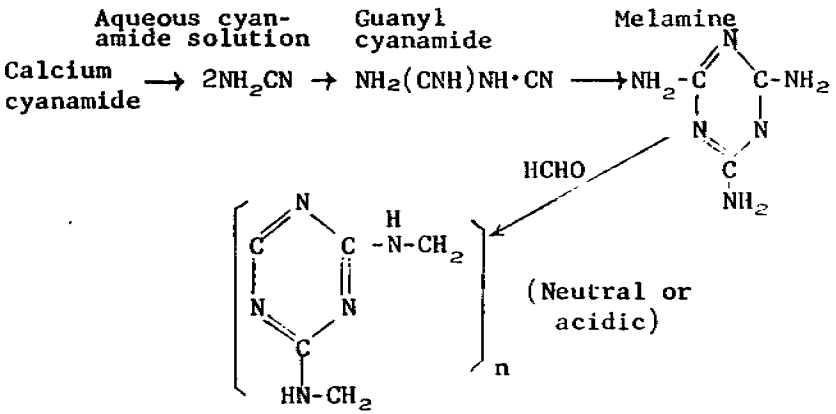
2. RAW MATERIALS

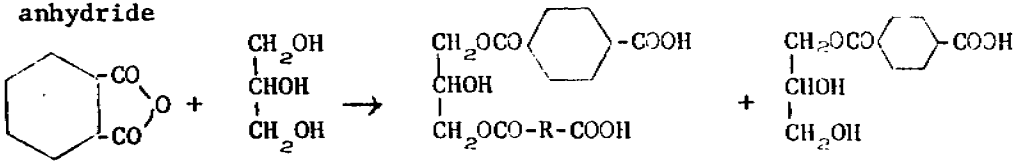
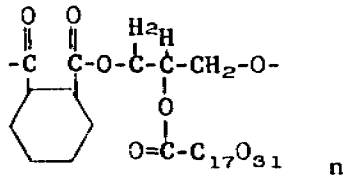
1) Formalin : Besides being used as the raw material for production of carbonate resin, urea resin and polyurethane, formalin is frequently utilized in the process for production of melamine polymer and for acetalization of polyvinyl alcohol.

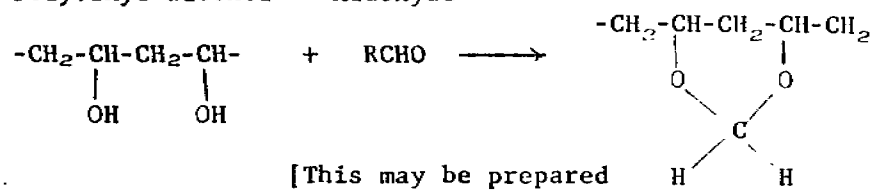
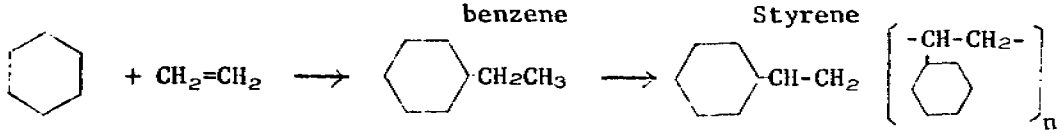
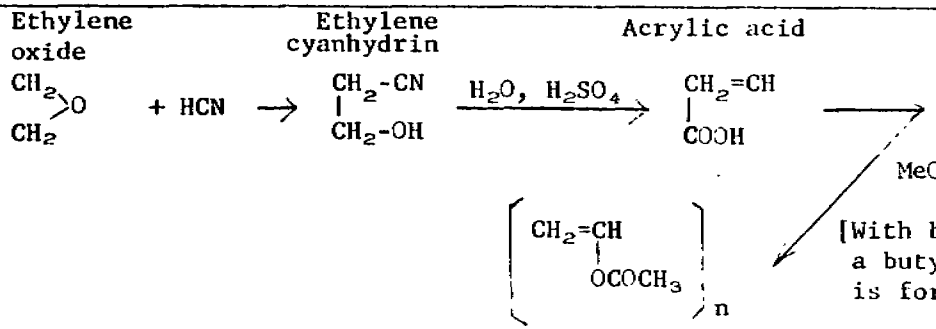
As a proof to show that the problem of formalin has gained importance in U.S. where the synthetic resin industry has seen a rapid upsurge. I will like

RODO KAGAKU, Volume 33, pages 1 - 22(1957).

TABLE 1 SUMMARY OF THE PROCESSES FOR MANUFACTURE OF SYNTHETIC RESINS

NAME	PROCESS	REMARKS
Phenol resin	Phenol + Formalin 	The resol(an initial condensate)is used for paint, adhesive, and final condensate (resit) is used for electrical part and equipments for chemical industry.
Urea resin	Urea + Formalin 	Wood adhesives, textile finish, electrical parts, building materials
Melamine resin	Aqueous cyanamide solution / Guanyl cyanamide / Melamine 	Plastics, paints, adhesives, textile finish

Alkyd resin	Phthalic anhydride + Glycerol →  [The material is cured by replacing a portion of the phthalic acid moiety with oleic acid or linoleic acid] 	Heat-curable, heat-non-curable, and acid-curable resins are available. For paint, plasticizer, mica, and adhesion of asbestos
Vinyl chloride resin	Acetylene $CH{\equiv}CH + HCl \longrightarrow \left[\begin{array}{l} CH_2{=}CH \\ \quad\quad\ \ Cl \end{array}\right]_n$ [Frequently used for copolymers]	Cable cover, oil pipe, and transport pipe for acids. Acid-resistant inner lining, film, meat
Vinyl acetate resin	Acetylene + Acetic acid $CH \equiv CH + CH_3COOH \longrightarrow \left[\begin{array}{l} CH_2{=}CH \\ \quad\quad\ \ OCOCH_3 \end{array}\right]_n$	VC/VA copolymer is used as pigment. For adhesion, finish, and cementing of glass. Raw material for making polyvinyl alcohol
Polyvinyl alcohol	Polyvinyl acetate is hydrolyzed with an acid or an alkali (No monomer is formed) $-CH_2-CH(OCOCH_3)-CH_2-CH(OCOCH_3)-CH_2-CH(OCOCH_3)- \xrightarrow[CH_3COOH]{H_2O} CH_2(OH)-CH-CH_2(OH)-CH-CH_2(OH)-CH-$	Adhesives, oil carrying pipe, raw material for acetal resins

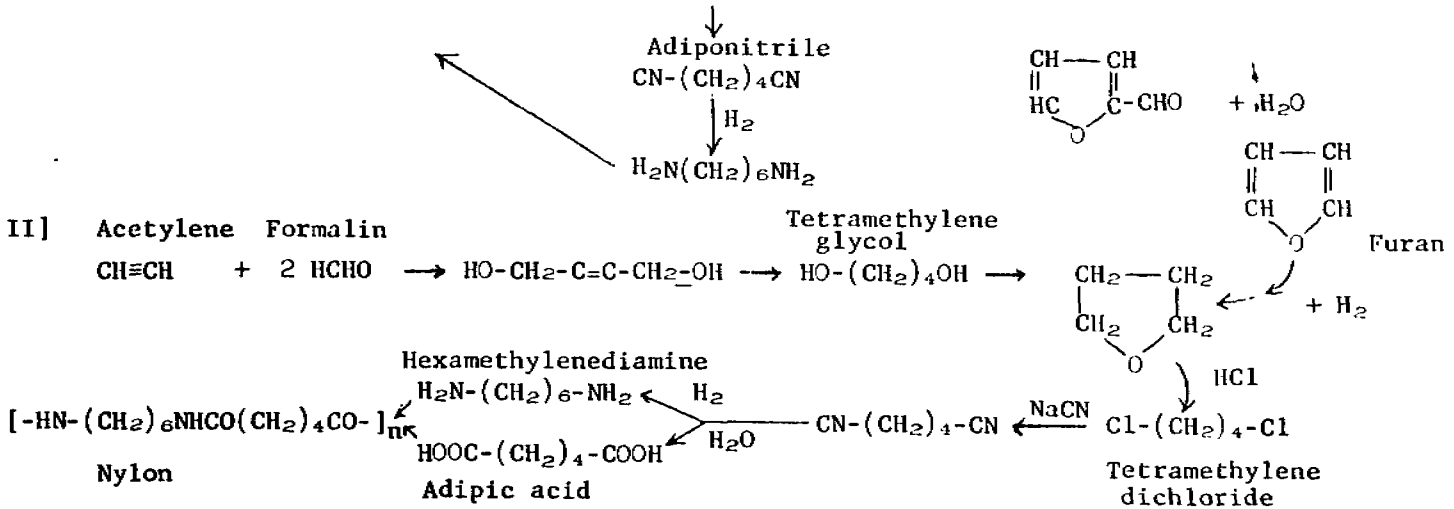
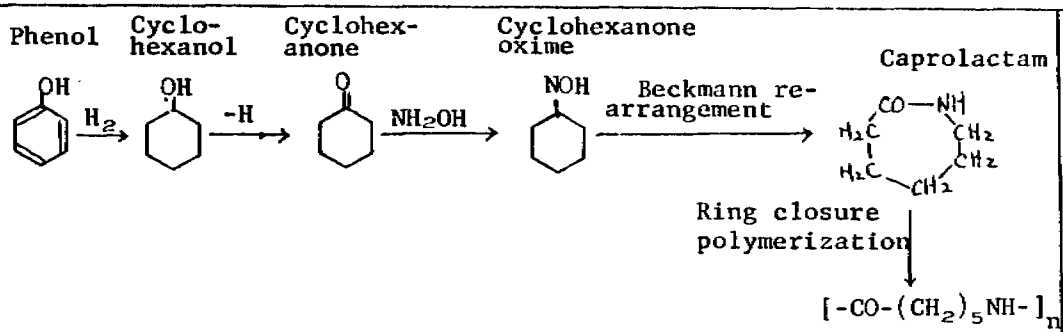
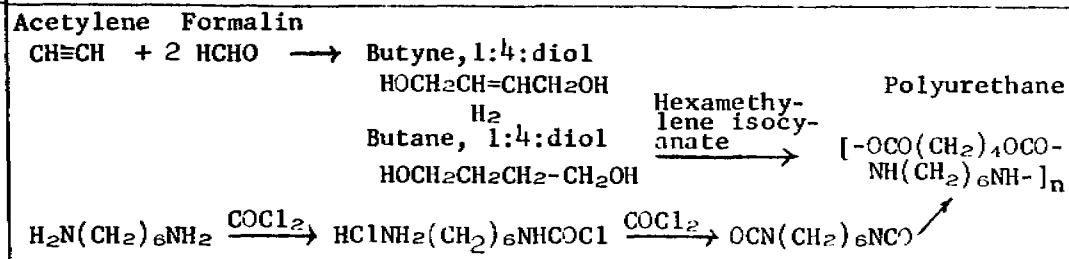
Polyvinyl acetal	Polyvinyl alcohol + Aldehyde  [This may be prepared directly from vinyl acetate resin]	Vinylon, wire laminates, textile additives, plastics
Polyethylene	$n(H_2C=CH_2) \longrightarrow (-CH_2-CH_2-)_n$ (poly-addition products)	Low pressure polymerization : lubricants, medium grade waxes High pressure polymerization : high frequency insulator, acid-resistant and oil-resistant inner lining
Polystyrene	Benzene + Ethylene → Ethyl benzene → Styrene 	High frequency insulator, clear molded products. Copolymerize with butadiene to make synthetic rubber.
Acrylic ester resin	Ethylene oxide + HCN → Ethylene cyanhydrin → Acrylic acid  Methyl acrylate, ester	Adhesives, paints, wire laminates, methyl ester

Methacrylic ester resin	Acetone + HCN → Acetone cyanhydrin (CH_3)$_2$C(OH)CN $\xrightarrow{-H_2O}$ $CH_2=C(CH_3)_2$ ⋯⋯ / Methanol (ROH) $CH_2=C(CH_3)COOR$ → $\left[-CH_2-C(CH_3)(COOR)-\right]_n$	Paint, adhesion, and the methyl ester is used for the window glass of aircrafts (Organic glass)
Silicone resin	(Grignard's process) $SiCl_4 \xrightarrow{RMgCl} RSiCl_2, RSiCl_3$ (Direct process) $Si \xrightarrow{RCl} R_2SiCl_2, RSiCl_3$ $R_2SiCl_2 \xrightarrow{H_2O} [R_2Si(OH)_2] \longrightarrow \left[-Si(R)_2-O-\right]_n$ $RSiCl_2 \xrightarrow{H_2O} [RSi(OH)_3] \longrightarrow \left[-Si(R)-O-\right]_n$	Paints, greases, lubricants, electrical insulator Oil for diffusion pump

TABLE 2 SUMMARY OF THE PROCESSES FOR MANUFACTURE OF SYNTHETIC FIBRES

NAME	PROCESS	REMARKS
Vinyon	Acetylene + Acetic acid: $CH \equiv CH + CH_3COOH \longrightarrow CH_2=CH-OCOCH_3$ Acetylene + Vinyl chloride: $CH = CH + HCl \longrightarrow CH_2=CHCl$ Copolymerization → $-(CH(OCOCH_3)-CH_2-CHCl-CH_2)_n-$	Filter cloth, laboratory coats, others
Rhovyl P, C, fibre	Acetylene + HCl → Vinyl chloride (CH_2CHCl) → (Heat with catalyst) → Polyvinyl chloride $(-CH_2-CHCl-)_n$ $(-CH_2-CCl_2-CH_2-CHCl-)_n$ Dissolve in acetone → P.C. fibre Dissolve in a solvent containing CS_2 → Rhovyl	Filtering cloth, packing materials, Insulating materials
Vinylidene chloride fibres, Salan Belon	Ethylene + Cl_2 → 1,2-dichloroethane ($CH_2Cl \cdot CH_2Cl$) + Cl_2 Acetylene + HCl → CH_2CHCl + Cl_2 Trichloroethane ($CH_2Cl \cdot CHCl_2$) $\xrightarrow[Ca(OH)_2]{-HCl}$ Vinylidene chloride (CH_2CCl_2) Lime milk	Screen, racket string, sheets, umbrella. Filtering cloth, shoes, handbags
Vinylon	Polyvinyl acetate $-(CH_2-CH(OCOCH_3)-CH_2-CH(OCOCH_3))_n-$ → (Saponification) → Polyvinyl alcohol $-(CH_2-CH(OH)-CH_2-CH(OH))_n-$ → (Thermal spinning) → HCHO $-CH_2-CH(O-CH(H)-O)-CH_2-CH-$	Cloth fabrics, socks, fishing nets, filtering cloth, and others

Arlon	Ethylene $CH_2=CH_2 \xrightarrow{Cl}$ CH_2OH / CH_2Cl (Ethylene chlorohydrin) $\xrightarrow{NaCN}$ CH_2OH / CH_2CN (Ethylene cyanhydrin) $\xrightarrow{-H_2O}$ CH_2 / $CHCN$ (Acrylonitrile) Acrylonitrile → Polymerization → Polyacrylonitrile → Spinning → Arlon	Umbrella material, curtains, tents, overcoats, etc.
Dynel (Chemstrand)	Acrylonitrile $CH_2=CHCN$ (4) Vinyl chloride $CH_2=CHCl$ (6) → Copolymerization → Dissolved in acetone → Dry spinning → Dynel Chemstrand is formed by copolymerization of acrylonitrile and vinyl acetate, followed by saponification. Acryronitrile that has fast polymerization rate is always added, and a monomer composition is constantly adjusted to prepare a acetone-soluble copolymer having uniform composition, and this product is Vinylon N.	
Nylon Perlon T	Adipic acid[$HOOC(CH_2)_4COOH$] and hexamethylenediamine [$NH_2(CH_2)_6NH_2$] were reacted to prepare hexamethylene diammonium adipate which was then polycondensed to form Nylon Two industrial processes are available. I] Phenol → (H_2) → Cyclohexanol → (OH_2) → $HOOC(CH_2)_4COOH$ → (Dehydration, NH_3) Aniline → (H_2O) → Cyclohexyl amine $HOOC(CH_2)_4COOH$ → Hexamethylene diamine $[-OC(CH_2)_4CONH(CH_2)_4NH]_n$	Lady's stocking, lace, groves, rain coat, velvet materials

Nylon (Continued)	
Amylan Perlon L (Igamide)		Same as Nylon
Polyurethane fibres Perlon V (Igamide V)		Acid-resistant filter paper, power belt, cord, insulation cable, etc.

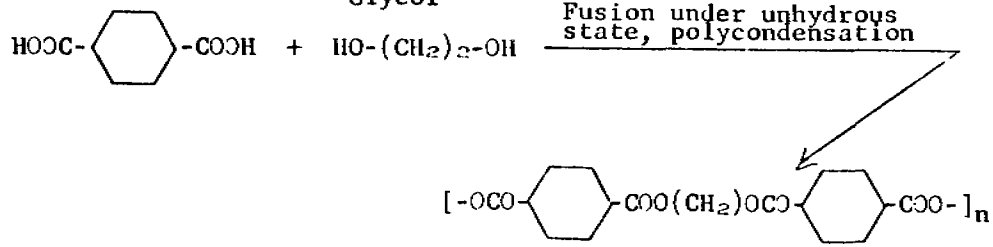
Terylene	Terephthalic acid + Glycol → Fusion under unhydrous state, polycondensation 	Filter paper, tire cord, screen, tent, etc.

TABLE 3 Change in the tolerance level of formaldehyde reported in U.S.

Year	Reported by	Tolerance level
1940	State of Massachusetts	20
1942	American Standard Association	10
1944	National Safety Council	10
1945	U.S. Department of Labor	10
1947	Silbermann*	10
1948	Dalla Valle*	20
1949	Patty*	10
1950	Elkins*	5
1952	A.C.G.I.H.**	5

* The author of the report

** A.C.G.I.H. = American Conference of Governmental Industrial Hygienists.

to show how the tolerance level of formalin has changed in the U.S.. (Table 3). The so-called "tolerance level" commonly used by the scientific community is not an absolute one. Rather, it is estimated from the results of animal tests or based on experience, and it shows the estimate of the limit that allows a workers to work for a long period of time under such environment without harm. Therefore, if the dose increases abruptly and if the daily working time is extended, poisoning or occupational disease may occur in the working environment that may not show any harmful effect otherwise. In other words, "tolerance level" has to be viewed more carefully. As more knowledges are acquired, generally the tolerance level has a tendency to decrease. Thus, if we look at the change of the tolerance level of formalin in the U.S. in recent years, during 10 year's period it has declined from 20 ppm to 5 ppm, and this is surprising and interesting. There is no other example in the history to show such a rapid change of the tolerance level in such a short period of time. This seems to indicate the enormous concern shown for formalin.

This tolerance level of formalin is the level when formalin gas is inhaled. There is also a report of a lethal dose of formalin by injection. Thus, the LD_{50} which is sufficient to kill 50 % of rats is 5.6 mg. Furthermore, most of the animals died within 30 minutes. But, naturally, needless to say that the actual occupational disease caused by formalin is caused by gas inhalation, rather than by a direct injection of formalin into body.

Formalin gas is extremely irritating, and even a trace amount can be detected easily. Therefore, severe harm is usually rare. But, in reality, formalin has been reported to cause dermatitis or inflammation of eyes, and therefore it requires precaution. Inflammation of respiratory tract can also be caused by formalin.

Earlier, we have investigated the effect of formalin gas on human body in a plant that carried out acetalation of polyvinyl alcohol. According to that results, following summation can be made.

(1) Many cases showed irritation of throat, bronchi and mucous membrane of eyes or disturbance of the digestive tracts. The frequency of complaint was 1.9 per person.

(2) The workers exposed to formalin gas frequently showed irritation of bronchi and mucous membrane of the eyes. With those workers who contacted directly with formalin water, more cases of skin disturbance were reported.

(3) The formalin gas concentration in the atmosphere of this plant was in a range of 6.5 - 13.14 ppm.

Recently, Professor Sugai of Kyushu University has reported the disease of eyes caused by formalin. They are as follows. The plant investigated was a plant that manufactured formalin, where the formalin concentration in the air was in a range of 3.7 - 27.8 ppm. Thus, the condition seemed to be worse than the above-said case.

Hyperemia was noted in conjunctiva of all of the workers. Eight out of 21 workers showed deposition of pigment along the cleavage of the eyelid. The number of bacteria in the fornix conjunctivae occurred in 1/3 of the members, and 1/4 of the members did not show any bacteria at all. However, there was almost no subjective symptoms. About 1/3 of the workers showed contraction of visual field and two members were proven to have relative central scotoma.

Eye drop experiments were carried out with rabbits, and following results were obtained.

When formalin water at a concentration exceeding 1000 times the acceptable level was applied 2 - 3 times, the bacteria in the eyes were killed, but there was no

obvious symptoms. With more than 100 fold concentration, some symptoms were shown, but the animals soon became accustomed to it. With more than 10 fold concentration, strong reaction was noted.

When rabbits with previous history of exposure to formalin were used to run eye drop test, meiosis occurred. This can be explained by the paralysis of the sympathetic nerves and the irritation of the terminals of the eye nerves.

Besides this, another literature[5] cautions that reticulocytes may show an increase when formaldehyde poisoning is induced in animals.

There were no recent reports about formalin dermatitis. But, I will like to note that formalin allergy is an established fact for a long time.

2) Phenols : Besides being used for making phenol resins by addition/ condensation with formalin, phenols are well known as raw materials for production of Nylon and Aramine.

Phenol has been known for a long time as a potent antiseptic which has been used widely in medical field.

On the other hand, phenol is also toxic to human body. Particularly, concentrated phenol can precipitate proteins. It is volatile and can easily penetrate into cells. It causes a severe pain in the site of its application. It can quickly paralyze the sensory nerves, and therefore phenol is used frequently for cleaning the ulcerous surface.

About 1/4 of the phenol entered the body can be oxidized, but the remainding 3/4 is known to be excreted in urine within 24 hours.[6] In this case, about half of them are excreted in free form and the remaining half are excreted in conjugated form. Among the conjugated phenols, 50 % are conjugated with sulfate, 30 % are conjugated with glucuronic acid and the remainder are conjugated with other acids.

When absorbed, phenol shows a toxic symptoms such like headache, drunkenness, change of respiratory rate, and rarely an intermittent spasm. Since it can stimulate and irritate the kidney when excreted into urine, it can also cause nephritis. Phenol can also be excreted into bile juice and also in the respired air to cause inflammation of the liver and lung.

When a sugar-containing lime is allowed to react with phenol, it precipitates the phenol, and thus this can prevent the absorption of phenol.

In the working site, phenol allergy is an important occupational disease. This allergy usually continues for several months, and thus can delay the workers from reporting back to work.

Since phenol has sensory paralysis effect, the patients may not be able to complain. This point requires particular caution.

3) Phthalic anhydride : Phthalic anhydride, along with glycerol, is used as raw material for production of alkyd resins. A portion of phthalic acid is substituted with oleic acid or linoleic acid to obtain a cured resin.

The major concern is the phthalic anhydride which contains small amounts maleic acid and naphthoquinone. Some symptoms attributed to phthalic acid may be due to these mixtures.[9]

Phthalic acid can irritate skin and mucous membrane. Inflammation of upper respiratory tract and inflammation of the eyes, and rarely bleeding from nose and blood in sputum were found in 14 patients who had visited the clinics of the plant in U.S.A. The patients were particularly annoyed by a constant coughing during night. Some showed symptoms of emphysema and bronchitis. Typical cases were found with the workers who had worked continuously for 1 - 7 years in the plant.

Phthalic acid combusts above 500°C, and therefore there is a danger of ignition. In this plant, there have been 3 accidents of this nature, resulted in one death.[10]

Kühnl[10] has proposed that 0.03 g/m^3 should be regarded as the tolerance level because irritation of mucous membrane starts at this level. Later, Menschick[11] has seen severe case of asthma and also found that those school children who had to go to the school near the plant handling phthalic acid frequently had conjunctivitis. Based on this evidence, Menschick proposed that the tolerance level had to be less than 0.025 g/m^3. He reported that various diseases were found among 18 workers out of 71 workers. The symptoms were the decrease of blood platelet counts, increase of white blood cell counts, increase of acidophile counts, increase of reticulocyte counts, decrease of serum Ca and P, and increase of total serum protein contents. Also, 21 out of 31 patients showed lower resistance of the blood vessel wall. Decrease of blood pressure during exposure to phthalic acid was noted in 41 out of 43 workers. There was enhanced tendon reflex, and dermatitis was also seen. Asthma, which was of particular concern to the investigator, was found in 4 out of 71 workers. The workers who had shown these symptoms had worked in the plant for few days to 20 months.

Vanadium pentoxide is used as the catalyst in the manufacturing process. According to the study, contact with vanadium pentoxide was said to increase the susceptibility to phthalic acid.

In Japan also, Kido[9] has reported that 18 out of 20 workers had dermatitis during two years of investigating period. According to the results of the patch test conducted on these workers, they were negative against pure sample of phthalic acid, but was strongly positive to industrial grade of phthalic acid. Based on this evidence, he claimed that the mixture, particularly naphthoquinone, is toxic.

Recently, we have pursued accidental cases of several workers who had to perform a job of polishing after coating the automobile body with resin paint and resulted in severe dermatitis, and found that the free phthalic acid remained in the phthalic acid resin was the cause.

In this particular incident, phthalic acid resin varnish was used in the color developer of the pigment. Besides this, toxicity of zinc chromate also was casted as a problem. However, later analyses of phthalic acid and zinc chromate revealed the presence of about 1 % of phthalic acid and 0.03 g of zinc chromate per 5 g of the sample. In a strict sense, therefore, the toxicity may have to be attributed to the synergistic effect of both. In any rates, it is important to note that phthalic acid has participated in this incidence. The phthalic acid in this pigment was proven only after heating the pigment at 120°C. Therefore, it is significant that phthalic acid can remain in the pigment in an amount far exceeding the amount expected.

4) Maleic anhydride : Tanaka has classified maleic acid's utility as follows.[13,14]

(1) For production of alkyd resins for paints(maleic acid resin, terpene/maleic anhydride resin).

(2) Production of maleic acid-treated oils.

(3) Production of hetero-polymer by copolymerizing with styrene, vinyl chloride, vinyl acetate, methyl methacrylate, acryl alcohol, to be used for production of heat-curable resin, particularly for paints, adhesives, dispersing agents,

viscosity regulating agent, and agents for treating of fibres.

(4) For sulfurization of polyester rubbers and tartaric acid.

Toxic symptoms by maleic acid were reported in recent years, mainly in the industry that has to do with synthesis and printing industry.

Frequently the areas contacting directly with maleic acid such like eyes and skins are affected. Naturally, inhalation of high concentration of maleic anhydride gas can cause inflammation of the upper respiratory tract.

Drug-induced inflammation of eyes were reported. According to the results of animal experiments, administration of 0.5 % aqueous solution can cause mild conjunctivitis and corneal opacity, and exposure to a gas(54.9 mg/m^3) for 1 hour can cause the same symptom in 50 % of the animals.

Ohwada[15] has run an experiment on the effect of maleic acid on skins. The chemical was prepared as an ointment in lanolin. After storing for 4 days, the ointment was painted on the fron arms, and the results were read after 6 hours. Under this condition, the ED_{50}(the concentration at which 50 % of the subjects showed positive) was 2.1 %. After storing the ointment for few days, the potency seemed to declined gradually. If the ointment was tested fresh, ED_{50} was 0.53 % and ED_5 was 0.07 %. Based on this result, I consider that persons sensitive to maleic acid can be detected if 0.07 % was used fresh.

5) Chlorine gas : Poisoning by chlorine gas has been known for a long time. Chlorine gas was used as poison gas in the World War I by Germany (April 22, 1915), which made it famous.

In the manufacturing industry, chlorine and the chlorine-containing bleach are used in decolorization and disinfection. Since a danger of poisoning exists in bleaching plant and the plants that electrolyze NaCl and potassium chloride, poisoning may also occur during the disinfection operation in a laundry plant, bleaching of jute, animal hairs and straws, and bleaching of paper. In chemical laboratory also, poisoning by chlorine gas can occur frequently. In recent years, personnels from artificial resin manufacturing plants(vinyl chloride plants) or water work frequently visited us for consultation about this problem.

As indicated in Table 4, there are many studies about the toxicity of chlorine gas.

The tolerance level of chlorine gas is indicated in Table 5. Most of the countries in the world set the tolerance level at about 1 ppm. According to Patty[16], 13 states in the U.S.A. adopt 1 ppm as the tolerance level. In Ohio and Washington, it is 5 ppm. Dalla Valle, however, claims that it has to be less than 0.55 ppm.

Symptoms of the acute chlorine poisoning are mainly the irritation at loci of the mucous membrane in contact with chlorine gas. Thus, depending on the extent of its exposure, bronchitis, pneumoniae, edema of lung and bleeding in lung may occur.

If a large amount of chlorine gas comes into contact, naturally the worker will lose his conciousness and may die.

If a person constantly contacts the gas, he or she may become accustomed to it and eventually can withstand a higher dosage of the gas. This does not mean that the person has become resistant to the gas, but rather he has lost his responsiveness to the gas. It has to be cautioned that, because of this oversight, one may show no symptom after inhaling a large dose of the gas but may bleed from the lung 2 - 3 days later and lose his life.

TABLE 4 Toxicity of chlorine gas on human body

mg/Litre	ppm	Symptoms
0.001	0.35	Will feel the effect after few hours of work
0.003	1.0	Tolerable limit (long term)
0.003 - 0.006	1.0 - 2.0	No significant symptoms after 6 hours of work
0.01	3.5	Feel the odor. No serious symptoms after 1/2 - 1 hour of work
0.012	4.0	Endurable limit after 1/2 - 1 hour of work
0.04	14.0	Medium degree of irritating symptoms
0.04 - 0.06	14.0—21.0	Danger to life after 1/2 - 1 hour of work
0.08	28.0	Cough and irritation
0.1 - 0.15	35 - 50	Death immediately or after 1/2 - 1 hour of work
2.5 - 2.8	900 - 1000	Immediate death

mg/litre = Amount in mg per liter
ppm = Parts per million

TABLE 5 Tolerance level set by law

Japan	Labor Law	1.0 ppm
U.S.A.	State of Massachusetts (1940)	1.0 ppm
"	Department of Public Health and Bureau of Mines	1.0 ppm
"	Lehmann and Hess	about 1.5 ppm
"	Conference of Plant Hygiene Inspectors (1947)	2.0 ppm
"	State of California(1948)	1.0 ppm
"	Conference of Plant Hygiene Inspectors	1.0 ppm

TABLE 6

mg/litre	ppm	Subjective observation	Reaction to potassium iodide paper
14.3	5000	Typical chlorine odor, green gas	Changes blue immediately
1.43	500	Significant chlorine odor, green gas	Changes blue immediately
0.143	50	Medium degree of chlorine odor, colorless gas	Changes blue immediately
0.0143	5	Weak chlorine odor	Changes blue in 3 - 5 sec
0.00143	0.5	No odor	Changes blue after 10 sec. or unchanged after 30 sec.

Because a change was seen in the liver and kidney of the rabbits poisoned by chlorine gas, some investigators have focussed their attention on the diseases that might be caused by chronic absorption of this gas.

There are many ways for determining the concentration of chlorine gas in the air of the working environment. Usually, the odor will tip off the workers. As indicated in Table 6, it will be convenient and practical to run a test with a potassium iodide paper and also by detecting the odor.[17]

Following steps have to be taken, when unfortunately a chlorine gas poisoning takes place.

(a) Move the subject to a gas-free environment to inhale fresh air. The subject has to be moved slowly into a warm room with fresh air. The rescurer should not panick, but has to have enough self protection before making a rescue.

(b) The subject has to be kept warm enough to the degree of sweating, but never apply a pressue on the chest.

(c) The cloth that has contacted the concentrated gas should be removed and replaced with new cloth(since the irritating gas usually has low volatility and high adsorbability, it may remain in cloth and hair to evaporate slowly and prolong the poisoning. Particular precaution is required if the room has poor ventilation). However, it has to be remembered that it is more important to keep the subject calm than to forcefully change the cloth of the afflicted subject.

(d) The patient has to be laid down, while raising the upper part of the body.

(e) Thick coffee or tea may relax the state of irritation.

(f) The patient has to be kept still and warm, to prevent pneumoniae.

(g) Treatment for the symptoms(it is best to treat the patient under doctor's supervision. In the following procedures, those with * mark should be performed only by physicians).

Treatment:

1. Mild poisoning : Make the patients smell the vapor of the equal mixture of alcohol and ether(In the old days, small amount of aniline vapor was used for this purpose, but this method is now considered to be dangerous).

   * Drink a very small amount of the mixture of alcohol, ether, and dilute ammonia(do not give alcohol or wine, merely to invigorating the patient)

2. Serious poisoning:
   * Venesect 500 - 800 cc of blood, depending on the build of the patient.
   Oxygen inhalation(with 5 % CO_2 added).
   Promote sweating
   * Cover the chest with cold wet cloth.

3. Eye injury :
   Wash with a large amount of water (do this with utmost urgency)
   Wash with 3 % boric acid solution or physiological saline warmed to body temperature(a tea spoonful of table salt is dissolved in 0.5 L warm water of about 37°C)
   * Rub with vaseline
   * Treat with codeine.
   Use of tight-fitting bandage is prohibited
   Avoid exposure to light

4. Against coughing :
   * Use codeine.

5. Against swelling of the mucous membrane:
   * Use coccaine or adrenaline.

6. General care :
   Take fluid food such like milk, egg and soup
   * Take or inject Hypo.

6) Acetic acid

Acetic acid serves as a starting material for production of vinyl acetate. Vinyl acetate is copolymerized with vinyl chloride, or polyvinyl alcohol is obtained from polyvinyl acetate.

Acetic acid, regardless of its wide industrial uses, has low incidence of poisoning. However, recently in Italy, acetic acid has been added to a list of occupationally hazardous substance(1932). Parmeggiain et al.[19] have surveyed the workers who had been working for more than 12 yrs in acetic acid plant, and found swelling of skin, tearing of skin with pain, reddness of eyes and mucous membrane of the throats, and in some cases a chronic bronchitis image by chest X-ray. Acidic tooth decay was also seen. And, symptoms in the digestive tract caused by unknown reason was also observed. These workers have been exposed almost constantly to 26 - 75 ppm of acetic acid gas. In some cases, the workers were exposed to the environment where the workers had a possibility of inhaling as much as 260 ppm of the gas. The tolerance level for acetic acid is set at 10 ppm.

7) Cyanide

Chance of using cyanide in synthetic resin industry is numerous in the production of acrylic and methacrylic resins. There is also a possibility of the danger of generating cyanide gas in the production of adiponitrile which is the intermediate for the production of nylon. Since cyanide is well known for its toxicity, usually any reactions that involve this gas are run in a completely enclosed system, so that there is no danger of coming into a direct contact with the liquid that contains cyanide compound or no danger of the gas leakage. It is, however, still possible that the gas can leak from the cyanide storage tank or the liquid may escape by accident to cause poisoning. Such accident occurs occasionally during the repair operation of the equipments. Recently, there were cases of cyanide poisoning in Japan. In one case, the accident occurred during the work to stop the leakage from the cyanide generator, and in the other, it occurred during removal of a product from the calcium cyanide manufacturing plant. Although four persons in the former case and one person in the latter case suffered from poisoning, fortunately there was no death. In another case, which occurred in another plant, poisoning resulted in death. In this case, after repairing the leakage of the calcium cyanide kettle, the test showed that the leak was not stopped. The worker panicked and tried to run and his leg was sprayed with cyanide gas. After running for about 20 m, he was exhausted and died. In this case, three other workers tried to remove the victim's pants and also suffered heavy poisoning.[20]

There are many books describing about how to handle and treat such acute poisoning with cyanide, and therefore, we are not going to repeat the procedure here. But, it might be necessary to mention about the works done in recent years that relate to the possibility of chronic cyanide poisoning.

When cyanide is detoxified, it binds with sulfur to form SCN, and rhodanase is the enzyme that catalyses such reaction. If the rhodanase enzyme is weak or inactive or if the supply of sulfur is not sufficient, the amount of rhodan being excreted into urine will decrease. On the other hand, if the above conditions are satisfied, the amount of urinary rhodan should increase with the amount of cyanide that has been acted upon. Therefore, if the amount of urinary rhodan in the urine of workers is constantly monitored, it should be possible to estimate the effective dosage of cyanide and the degree of detoxification. In recent years, many companies use this rhodan test.

However, the level of rhodan may vary even if the worker is not exposed to cyanide. For example, cyanide in the cigarette can be detoxified in the body to increase the rhodan content in urine (or the rhodan contents in saliva and urine may increase).

Thus, a true picture may not emerge unless the fate and amount of urinary rhodan is traced constantly for the same person. Currently in Japan, no company is doing this.

Recently, a paper was published in Italy about the subacute and chronic poisoning by cyanide among people who were working in cyanide-related operation or accidentally inhaled cyanide gas. Symptoms such like vertigo, inbalance, problem in gastric tract, difficulty of inhalation in exercise, and pain in heart have been reported. Increase in hemoglobin contents or increase in lymphocytes due to "stress" has also been reported in literature[21].

We have observed an increase of the serum cholinesterase activity in person who has shown a symptom believed to be due to chronic poisoning by cyanides.[22]

Like the case with formalin, there is a trend in recent years to set a strict tolerance level for cyanide. This is perhaps one of the expression to show a tremendous increase in the demand for cyanide.

Thus, Sato[23] has carried out an experiment with mice to re-evaluate the existing tolerance level(10 ppm). He noted that a mild symptom was seen, even at 5 ppm. Based on this finding, he claims that, perhaps, a level of 2 ppm will be safe.

When a filter paper is dipped in a liquid containing a mixture of sublimate and methyl orange and this wet filter paper is brought into the plant location, presence of cyanide will cause the color of the filter paper to change into cherry red or red. If the color does not change within two minutes, it can be considered safe. Kitagawa's detection tube is also available.

8) Methyl acrylate

Methyl acrylate that serves as the starting material for production of acrylic resin shows irritating effect on skin, mucous membrane of eyes, nose, and respiratory tracts. Although the symptoms may appear at 30 ppm level(in air), this level will cause merely some unpleasantness and mild headache. Thus, at this level, there is no long-lasting problem nor cumulative effect.

If the concentration is higher than this level, it can cause, severe hyperemia of mucous membrane, epiphora, salivation, increase of running nose, and disruption of respiratory activity. It may eventually lead to convulsion or sleepness, respiratory paralysis and cyanosis, and finally to death. The disturbance of respiratory activity is said to be caused by the action of methyl acrylate on central nerve system.

Animal experiments showed that administration of 0.69 g per kg body weight of mouse can cause toxic symptoms.

Acute toxic symptoms will appear at an atmospheric concentration of 200 ppm. The odor can be detected at a level of 0.1 ppm. In the past, the tolerance level was set as 75 ppm. However, Takanarita[24] has cautioned that it should be lower than 50 ppm. However, since even 30 ppm can cause some mild symptoms, the tolerance level should be kept below this level for workers who have to work in such an environment for a long period of time.

When methyl acrylate is painted on skin, inflammation and edema is noted at the loci. In some severe cases, necrosis has been observed at the loci. Methyl acrylate has a tendency to penetrate deep into skin, and can cause allergy symptoms.

Kitagawa[25], along with Takanarita, has modified and improved the method for determination of the level of methyl acrylate.

Precautions needed in the handling of methyl acrylate:

(1) Due to its volatility, the work has to be done in a well ventilated room.

(2) If there is insufficient ventilation, the worker has to wear a gas mask filled with organic filtering elements.

(3) If the hand is contaminated, the hand should be dipped in a wash basin containing 0.05 % potassium permanganate solution which destroys the double bond of the methyl acrylate. The amount of potassium permanganate to be consumed is six times the amount of methyl acrylate, and therefore the above said concentration of potassium permanganate solution should be enough.

(4) Some people are sensitive to methyl acrylate. Therefore, a patch test should be used to screen the applicants and those with positive reaction should not be hired.

(5) Wear a rubber protective glove.

9) Urea

A portion of the toxicity of urine has been attributed to its urea content. Experiments with dogs or rabbits have shown that urea can cause tetani. With pigeon, 1/100th of the body weight, and with frog, 1/50th of the body weight can cause an increase in the blood urea content by interdermal injection, and can cause convulsion. It is also known that accumulation of urea takes place in the brain tissue during the convulsive disease.

The only occupational disease caused by urea was the change of skin, and not much has been studied about the disease caused by absorption of urea.

When urea comes into contact with hands and fingers, the skin surface will become thin and the finger print will become unclear. Then, it turns into red and loses senses. If urea reaches deep into the hand, it can cause bleeding and ulcer. Contact with urea, together with abrasion of skin, seems to cause the symptoms.

In one plant, examination of 48 workers revealed that 125 fingers were affected quite seriously, and 21 fingers per person were affected during this study period.[28]

The best way of prevention is to wear a glove. If the worker noted a contact with urea, he should wash the loci carefully with water each time and then wipe the area with dry towel. The glove should be washed frequently. Protective cream may also be coated on the hands. In such case, a film-forming type of cream such like Kanekutan D (vinyl chloride) or ethyl methacrylate may be used.

It is also possible to cover the hand and fingers with bandage, but this will lower the working efficiency.

It was reported that, when an ulcer developped, there was relatively little pus formation, perhaps due to bactericidal effect of urea.

10) Others

Since the discovery by Reppe in 1938 that acrylic resins can be synthesized from acetylene and carbon monoxide, nickel carbonyl has become a popular catalyst and attracted much attention. This nickel carbonyl is quite toxic, and has been the problem in Nagoya area. In fact, a company has dispatched their R and D personnel to our clinic for health check, because of the concern over such poisoning.[27] This has been reported in the paper by Nishikiori and Kawase.[28,29,30] Toxicity of disulfur decafluoride(S_2F_{10}) and tetraethylortho-silicates has also been studied.

3. MONOMERS

1) Vinyl chloride: Vinyl chloride has anesthetic property, but the toxicity is generally considered to be lower than carbon tetrachloride. Results of animal experiments gave the following indications.

20 - 40 %	Death in a short while
10 %	60 Minutes, danger to life
5 %	60 Minutes, symptoms appear
0.5 %	No symptoms after few hours

The tolerance level has been reported as 500 ppm.

In a plant in the Northeastern portion of Japan in 1954, few workers working in the production of vinyl chloride showed a Raynold syndrome-like disease. Thus, there was a numbing feeling in fingers and toes, the faces turned pale, indicating a problem in blood circulation, accompanied by loss of sensitivity and felt cold. The problem, however, disappeared before any causes could be found. Even today, the cause of this problem is not clear.[31]

2) Vinylidene chloride: Besides being combustible, vinylidene chloride is known to possess considerable degree of toxicity. It has an effect similar to ethylene chloride. A strong anesthetic action is shown at a level 4000 ppm. At 8000 ppm level, death occurs within one minute. Results of animal tests showed that it is safe at a level of 200 ppm for 8 hours and at a level of 1000 ppm for 30 - 60 minutes. At 250 ppm level, it shows a chronic cumulative effect. But, there is no such harm(no chronic effect) at 100 ppm. The tolerance level is set at 100 ppm. It has odor similar to carbon tetrachloride. At 1000 ppm, this odor is obvious, but at 500 ppm the odor is barely detectable. If there is a degradation product, even a smaller amount than 500 ppm can be detected by its odor.

Initial anesthetic symptoms are headache, vertigo, dryness of lips, loss of balance, and fatigue. Chronically, it shows symptoms such like headache, gastrointestinal problems, vomiting, looseness of the stomach and chest pain.

Since vinylidene chloride contains a phenolic polymerization inhibitor, the phenol may frequently cause irritation in skin or mucous membrane. The polymerization inhibitor usually exists in a quantity of 0.3 - 1.0 %. Without such inhibitor, explosion may occur after a short time of storage unless it is sheltered from air and light, because, in the presence of oxygen, it can form a peroxide of unknown structure, and this peroxide serves as a polymerization catalyst to cause a reaction. The peroxide is extremely explosive and is absorbed in the polymer to make it explosive. If the content of peroxide exceeds 15 %, drying the polymer can cause an explosion by heat or by mechanical shock. When the peroxide decomposes gradually, the final products will be formaldehyde, phosgene, and hydrogen chloride. Therefore, any sour odor associated with vinylidene chloride polymer will mean a danger.

Experiments have shown that vinylidene chloride can cause acute poisoning of liver and kidney. Pathologically, this is a toxic nephritis. Anuria will be the first stage of the poisoning. At this stage, in order to avoid hyderemia $\longrightarrow$ pulmonary edema, it is necessary to irrigate the peritoneal cavity with Ringer or Tyrode (modified) solution to regain the electrolyte balance of the blood.[32]

Last year, there was a case of neuritis optica axialis among the workers working in a vinylidene chloride manufacturing plant in Japan. So far, however, the cause of this disease has not been established.[33]

3) Acrylonitrile

Toxicity of acrylonitrile has been published before,[34] and therefore it will not be repeated here. The tolerance level is 20 ppm.

The toxic symptoms of acrylonitrile resemble that of cyanide, and in the past this was attributed to the formation of cyanide in vivo. In recent years, however, this possibility has been discounted. When acrylonitrile is hydrolyzed in acid or alkaline solution, it released ammonia rather than cyanide to become acrylic acid. When an amount of this compound equivalent to LD_{50} (i.e. 13 mg/kg) was given to animals and the dead animals were autopsied, the amount of cyanic acid found in the blood of heart was 0.09 - 0.280 γ/cc. This amount is too small, if we assume that all of the acrylonitrile administered have released cyanic acid. Medical treatment for cyanide poisoning (20 % dextrose 5 cc/kg, i.v.; 3 % sodium nitrite 70 mg/kg, i.d.) has been a failure. These evidences thus overturned the conventional concept.

Other higher nitriles are used more and more today. We have carried out experiments on palmitonitrile and other aliphatic nitriles about their toxicity. They can cause broad necrosis in the loci of injection, and can also cause coagulation and necrosis in liver and glass-like denaturation of the tubules of kidney. These evidences indicate that acrylonitrile has a sizable degree of local irritation and absorption toxicity. These higher nitriles have obnoxious odor which annoys the workers. So far, no satisfactory studies have been conducted on this aspect.[36]

4) Others : Styrene monomer also shows a high degree of irritating character. This has been reported in many books and therefore will not be repeated here.[26] There was a reported case of the disease of eyes caused by droplets from the splash of chloroacrylic acid.

4. POLYMERS

In view of the chemical properties, the so-called "polymers" usually do not have as much irritability and toxicity as the monomers.

Recently, however, new types of occupational diseases called by a name "polymer fume fever"[37] or "resinosis"[37] have been reported, and therefore they should not be overlooked.[38] They are the inflammation of upper respiratory tract, bronchitis or allergy-related fever caused by inhalation of a large amount of spray or powder dusts. They are more or less dependent on individual polymer, and are perhaps due to mechanical and physical disturbance.

One of the widely publicised disease of polymer is the problem of the skin irritation caused by wearing Nylon stocking. This is more of a public health problem than occupational disease problem, because the problem occurred with women who wore Nylon stockings. In fact, in 1940 when Nylon stocking was first introduced, it created an epidemic of Nylon dermatitis in the U.S.A.. Various tests were conducted. Particularly, the so-called Nylon patch test was developed and this method was used widely in an effort to find its cause. It was found that Nylon or its intermediate did not cause a positive reaction on skin, but the reaction occurred only with the stained Nylon. As a result, the Nylon dermatitis was attributed to the dyestuff used in Nylon, and this problem was solved. For example, in some reports, raw Nylon cloth was patched on the skin of 9 patients suffering from Nylon dermatitis but the reaction was negative, except 7 samples of stained Nylon cloth which showed severe reaction.[40] In another report, experiment gave the following results.[41]

	Test subjects	Positives
Nylon cloth only	42	0
Pyrrol derivative of Nylon	42	0
Dyestuff used in Nylon	42	2
Intermediate for the Dyestuff used in Nylon	42	6

This result indicates that contamination by dye itself , particularly by its intermediate, gave the strongest irritability. The cause was found in paraphenylenediamine or its homologs. Naturally, since Nylon prevents the evaporation of sweat, the situation is aggravated by a rash-like change. In addition, mechanical stimulus by Nylon can also enhance suppuration. Many reports claim that this type of dermatitis should be treated as an allergy-related dermatitis.

Literature on the irritability toxicity of individual polymers is relatively rare, except Nylon. In Japan, they are almost non-existing. Recently, we were visited by an official of a company who mentioned that two workers in a plant that used urea resin as wood cement suffered neurasthenia-like symptoms. In this case, however, it is not clear whether the urea resin was the cause or not.

Following literatures are available abroad.[42]

Ethylene tetrafluoride is an unstable, toxic gas, but its polymer also showed toxic effect.

Methyl methacrylate is a substance that can cause irritation in skin and mucous membrane. Similar symptoms were observed when the powder dusts of the polymer was inhaled for a long period of time. Naturally, the symptoms are very mild. Another property of polymethyl methacrylate is its ability to penetrate through the rubber covering. Therefore, this material can not be used for making a rubber glove.

Cpichlorohydrin is treated with phenol to remove the chlorine and then the resulted product is polymerized to make epoxy or epoxyd resin. Epoxy or epoxyd resin can irritate the skin by contact. In a manufacturing plant, 8 workers suffered from bulla-like inflammation on hand, head, eyes and other parts of skins in the first 4 months of the plant's operation.[43]

Poisoning or dermatitis by polypropylene (polyoxy propylene)-glycol, methyl polysiloxane[45], Teflon A[46], Paraplex G-25 and G-40 has also been reported in recent years.[7]

In many cases, however, symptoms which were originally atrributed to the polymers were later found to be caused by the solvents or additives present in the polymer.

During the polymerization of Nylon or during the spinning process, 0.1 - 1.9 ppm of diphenyl or diphenyl oxide may be discharged as vapor. Although this level does not seem to cause any serious problems, it can still irritate the eyes or the respiratory tracts.[48]

In the loading area of polyvinyl chloride, one may feel a mild irritation caused by the vinyl chloride monomer. Or, in the spinning room, one has a reason to concern about exposure to a low level of acetone and high level (25 - 200 ppm) of carbon disulfide. Since the tolerance level of carbon disulfide is 20 ppm, it is natural to

see a report that neurotic symptoms and irritation symptoms of mucous membrane were found among workers during one year period of operation.[49]

In the handling of polystyrene, one may be exposed to ethylbenzene. At 275 ppm level, it can cause symptoms such like neurological excitation, leukopenia and lymphocytosis. Dermatitis is rare. Also, aluminum chloride can cause a convulsive bronchitis or delay the heeling of wounds. If there is a possibility of the presence of the residue of styrene monomer, naturally this will be toxic. In fact, there is a report to prove the presence of about 200 ppm level of styrene in polystyrene. Based on these reports, the tolerance level of ethylbenzene was set 100 ppm and that of styrene was set 150 ppm.

There has been an example of the irritability of phenolic resin becoming a problem. In this case also, later work has found contamination by monomer as the cause.[51]

5. SOLVENTS

1) Mono, di, tri-propylene glycol methyl ether : This is the solvent for nitrocellulose or synthetic resins. It is not ferrocorrosive, is stable to heat, and can mix with other organic solvents.

The LD_{50} for rats is 6.6 cc with the monopropylene glycol, 5.4 cc with the dipropylene glycol, and 3.3 cc with the tripropylene glycol.

Symptoms do not appear, even after administering the mono substance at a daily dose of 1 cc for 5 days, up to 35 days.

When a large dose of mono or tripropyleneglycol methyl ether is painted on skin and allowed to absorb, it can cause an anesthetic death. With the same dosage of dipropylene glycol, however, such symptoms were not observed.

Naturally, with a very large dosage of mono-, di- or tri-propyleneglycol, it can cause depression of neurological function, and irritation of the mucous membranes of eyes, nose and lung.

It may be concluded, therefore, that a one time exposure to propyleneglycol methyl ether will not cause any symptoms, and this compound will be dangerous only when used continuously.

2) Dimethylformamide: This is used as a solvent of polyacrylonitrile.

A larger dose will be toxic enough to cause a death in animals. Symptoms are loss of body weight and hepatic disorder, but it does not show anesthetic activity.

In one spinning room, a level of 0.04 mg/litre was discovered. However, the workers working in this plant did not show any symptoms. A tolerance level has not been established, because this is a new substance.[53]

3) Methylethylketone(Butanone) : Concern about the disease caused by methylethylketone occurred mainly as a result of the appearance of Saran paints.

Saran paints are made of 80 % methylethylketone and 20 % salan. Its effect on living body has been attributed mainly to methylethylketone. Methylethylketone [$CH_3COC_2H_5$] is an aliphatic ketone. Generally speaking, the more carbon number the molecule has, the more toxic will be the compound. Based on this prediction, methylethylketone will be the second least toxic among some ten kinds of aliphatic ketones.

Main effect is the anesthetic effect on nerve system and the irritation of mucous membranes.

In actual cases,[54] headache, nausea, vomiting have been reported. In serious

cases, the victims may fall into comma. If left unattended, it may lead to respiratory paralysis and circulatory problem. However, no death has ever been reported. In the other countries, there was a case where women laborors working in the water-proofing project on raincoats were intoxicated and became uncncious, but later recovered without after effect. Methylethyl ketone(500 ppm) and acetone(450 ppm) were found in the air of this plant. However, in view of the symptoms, it is more likely that the air was filled with higher concentration of the gases. It was estimated that the concentration of methylethylketone was 1850 ppm and that of acetone was 1530 ppm.

Tolerance level of methylethylketone was set at 300 ppm. Haggard stated that presence of 1 - 2 g of methyl ethylketone in blood would start the toxic symptoms, 3 g would cause the loss of tendon reflex, 5 g would cause the loss of corneal reflex , and 9 g would lead to death.[55]

Results of the administration of methylethylketone to guinea pigs for 8 hours are shown below.

0.6 %....Irritation of mucous membrane

1.5 %....Anesthetic effect

2.0 %....Death

The magnitude of the acute effect of methylethylketone on human body is believed to be as follows.

0.3 %....Can withstand for 8 hours without signficant problem
1 %....Can withstand for 1 hour without significant problem
1.3-1.0 %..Danger to life after 4 - 8 hours
5 - 10 %...Danger to life after 30 - 60 minutes

4) Others : Few years ago, tetrachloroethane used for processing vinyl chloride caused two death by hepatic disorder in Tokyo area.[56] Besides, various other kinds of solvents, such like dioxane, benzene, tetrahydrofuran, formalin, acetone, and carbon dioxide are in use.

Toxicity of these solvents have been reviewed in other books, and therefore they are not repeated here. However, it is needless to say that these solvents play a great role in the toxification in synthetic resin and fibre industries, and this fact has to be always kept in mind.

6. ADDITIVES

Substances that are added in synthetic resins as plasticizers, stabilizers or color developing agent, may have toxicity.

Phthalate and phosphate are two substances that require particular attention. Well-known phthalates are dioctyl phthalate(DOP) and dibutyl phthalate(DBP). According to Carpenter[57] who has fed various amounts of DOP to rats, a level of 0.13 - 0.04 % did not cause any problems after 2 years. At 0.4 %, however, the % of weight increase was hampered, and hepatic and nephrotoxicities were observed. Based on this datum, he has set the toxic limit for rats as 0.06 - 0.2 g/kg/day(2 years feeding). With guinea pigs, 0.13 % DOP slightly enlarged the liver, but the disturbance was not severe. At 0.[illegible] %, DOP showed toxicity. With dogs, 0.06 cc/kg/day is believed to be the toxic limit.

DBP attracted the attention of the public because of the report of accidental poisoning.[58] A 23 year old worker took DBP mistakenly as a purgatives. He took a large spoonful of DBP at roon time and experienced nausea and vertigo. during the work hours. Few hours later, the eyes swelled and became painful with tears running. The victim visited the hospital next day, and diffusive edema, granular inflammation of cornea and centralized erosion were discovered. Protein, red blood cells and white blood cells were found in the urine. With therapy, a quick recovery took place and he was discharged 14 days later.

On the other hand, the important phosphate is tricresyl phosphate, and several cases of poisoning have been reported in Japan. Tricresyl phosphate(TCP) shows the toxicity characteristic to ortho compounds. The toxicity of metha and para compounds is known to be much milder. In the accidental cases in Japan, polyneuritis similar to infantile paralysis occurred. Since TCP is a substance to inhibit the true cholinesterase that is related to nerve functions, the sequence of the incidence of this disease is understandable. Agricultural chemicals such like parathion or TEPP are the well known cholinesterase inhibitor, and they are the same kind of organophosphate agents like TCP.

Thompson[60] has administered orally 1 cc TCP/kg to chicks in one dose and demonstrated the incidence of motor paralysis and demyelination in 12 - 15 days period. The serum(pseudo)-cholinesterase level declined rapidly to 1/4 of the normal level(same with the brain and nerve cholinesterases). Although the serum cholinesterase(ChE) level returned to normal level in 14 days, it took 21 days for the ChE of the brain and spine to return to the normal level. Based on these evidences, he made the following comments. Thus, the pseudocholinesterase rather than the true cholinesterase is affected by TCP, and the decrease of the ChE does not occur in parallel to the demyelination. Therefore, there is a need to pay an attention on other enzymes such like tributyrirase and its change. While 60 - 80 % of the pseudocholinesterase activity was inhibited by TCP, only 35 - 50 % of tributylynase was inhibited. Other investigators, however, claim the antigonistic effect of TCP against vitamin E. Therefore, we have to acknowledge that the true mechanism of the demyelination is still not clear.

In the reports published in Czechoslovakia,[61] autonomic nerve symptoms were said to be the major symptoms, and others were dermographism, mulnutritions, and blood pressure depression. Other nerve symptoms were polyneuritis(25 %), sleeplessness, headache, neurasthenia, extrapyramidal syndrome(mostly in older persons), and syndrome of the pyramidal tract. In this report, attention was paid to the relation between the route of invasion and the incidence of symptoms. In the case of invasion by absorption through the skin, symptoms of the peripheral nerve system are the most frequent. In the case of invasion by inhalation, attack on the central nerve system is the most frequent.

Recently, there was a report of poisoning by dibutyl tin dilaurate (Stabilizer No. 52) which was used as a stabilizer.[62] This substance irritated strongly the upper respiratory tract, turned urine to urobillinogen positive and showed a tendency to cause anemic symptoms in blood cells.

Experiments with rats showed a disorder appeared at 0.5 ppm. In this case, the incidence of symptoms was related to the humidity of the environment. It is interesting to note that this substance is harmful at temperature exceeding 30°C, but is not particularly harmful at temperature lower than 25°C.

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