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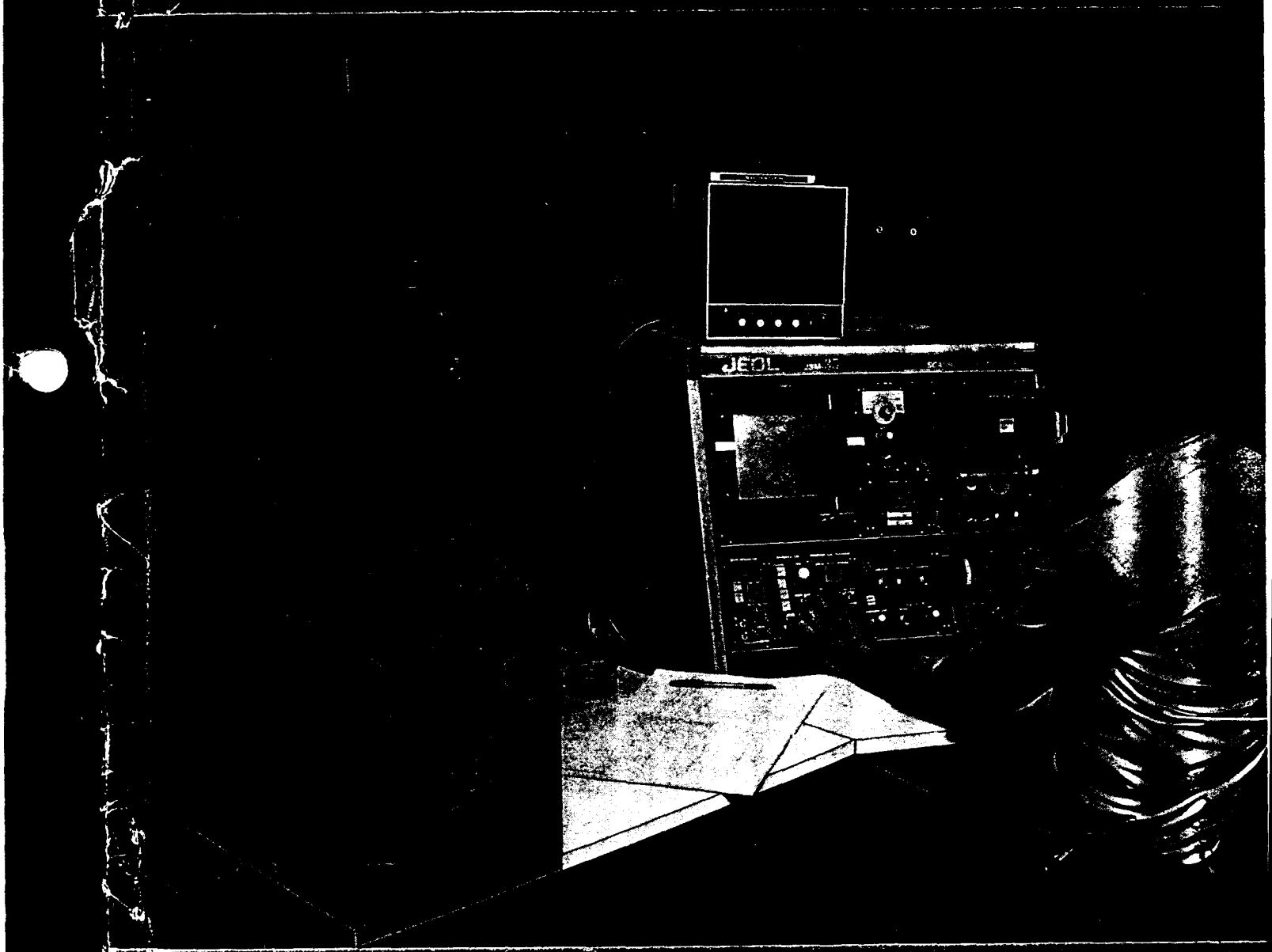

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Problems of hygiene maintenance for food coming into contact with rubber and plastics products

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(NO SUMMARY GIVEN)

1. INTRODUCTION

Recently concern has arisen over food safety, and over the question of containers, packaging and utensils used in contact with food products in general. Investigations have been carried out to decide whether there is a health risk in additives, using the results of investigations to determine three factors, i.e. the toxicity of additives, the amounts of migration of these additives, and the extent to which food products coming into contact with containers, utensils and packaging are consumed. To determine the toxicity of additives, three types of tests are employed, for acute, sub-acute and chronic toxicity (1). Previously tests which determined life or death after a large amount of the additive was given in a single dose, as in the acute toxicity tests, were regarded as important, but as amounts of materials migrating from packaging and utensils into the food products are in any case extremely small, and because of the limited extent to which acute toxicity can be used as a screening test, more recently sub-acute toxicity has been used, with a certain amount of caution, i.e. observing an adequate number of symptoms, and since chronic toxicity is predictable to a certain extent, a period of 90 days for sub-acute toxicity tests is now generally used in Europe. It has been reported that there may of course be a need to carry out chronic toxicity tests over a period of as long as 2 years if doubtful points arise. In the case of PVC and polyolefins, additives which are currently judged to be satisfactory, i.e. are drawn up on the positive list (PL), must meet five conditions. These conditions, which are strictly applied, are, in addition to the degree of confidence in the toxicity data, whether the substance in question is mentioned in positive lists abroad, whether there are cases of its use abroad, whether there are considerable advantages derived from the use of the substance as an additive and which can be universally agreed to, and whether in addition the use of the substance is kept down to its lowest limit of significance.

As regards migration of additives, it has become generally accepted that things which are highly toxic cannot be used even if they do not migrate completely. It may be said in fact that there is no trouble about using an additive if its toxicity is comparatively low and not much migration takes place. In some cases, e.g. when a container comes in contact with food products such as milk or frying oil, the actual food products may be used, but food products are not always quite so simple, but may contain highly complex materials, and since it is difficult to establish methods of analysis of migration, water, acetic acid, alcohol, *n*-heptane and similar solvents are used.

A major concern is the Acceptable Daily Intake (ADI). This value represents data obtained by careful examination of symptoms occurring with agricultural chemicals. A level is found below which no symptoms are observed in the most susceptible animals, and 1% of this is defined as the amount which is safe for human beings. With the exceptions of agricultural chemicals, carcinogenic materials and heavy metals, where the daily intake is less than 0.1 mg no hazard is presented. This value is known as the Frawley limiting value. Consideration of the carcinogenic nature of materials, of the foetal abnormalities caused by drugs containing thalidomide and of occupational cancer caused by materials such as aromatic amines, nitroso compounds and vinyl chloride monomer is also important in toxicity assessment.

High-molecular materials such as rubber are generally considered to be harmless, but because of their method of production they contain additional low-molecular materials such as residual monomers, solvents, and polymeric chemicals which create a toxicity problem. The rubber industry has a rich history, and its experience goes back more than 50 years, and inthis respect and others differs from the plastics industry. Plastics are used a great deal in packaging and containers, whereas the rubber products in this field are few, mostly pertaining to containers. By contrast with plastics containers and the like, where the area of contact with the medium is large and the time of contact is long, the majority of rubber products used in packaging and containers have a small contact area and a long contact time, such as packaging seals and crown top discs, or a large contact area and a short contact time, such as cups for milking apparatus and the like. Therefore it is not the case that tests can be carried out under the same conditions as for plastics. However, test conditions are very strict for products such as teats for babies' bottles, teething rings and closures for drug containers. We shall now consider the problems of hygiene relating to rubber and plastics products, paying particular attention to rubber.

2. GENERAL CONCEPTS OF TOXICITY (refs. 2, 3 and 4)

When we consider problems of hygiene relating to rubber and plastics, we use expressions such as 'toxic', but if these are to be understood their meaning must be defined in advance.

When a substance has a biological effect on a living organism, and this effect is unpleasant to the organism concerned, the effect is said to be toxic. There are also cases where the same biological effect is not necessarily considered to be toxic for our purposes, such as when this effect is the purpose of using the substance, i.e. in medical drugs. Generally, where a substance having a biological effect has been given to a living organism, the amount is classified as follows, on the basis of the reaction shown by the organism.

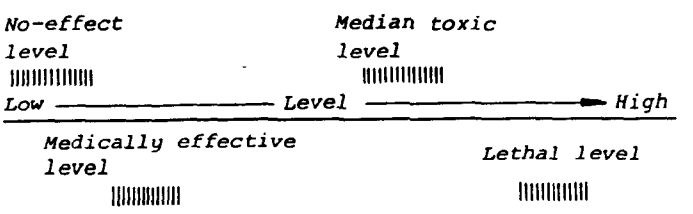

Figure 1 Effects on living organisms

No-effect dose: the amount which does not have any effect on the person;

Effective dose: an amount which produces some effect;

Medium toxicity: an amount which produces a severely unpleasant effect on the person concerned, without being lethal;

Lethal dose: an amount which causes the death of the person.

When a substance is given to a person and it produces a change in the work or functioning of that person it is said to have a biological effect. If we consider the case of medical drugs, which have a biological effect, the effects which an individual suffers vary according to the amount of the substance he is given. There are generally thought to be four dose levels; as shown in Fig. 1: the non-effect level, where the amount given is very small and no effect is observed; the medically effective level, where what effect there is is considered to be beneficial with regard to certain ailments; the medium toxic level, where the dose is large and the recipient is considerably harmed; and the largest dose, the lethal level, sufficient to cause death.

There are some substances which are harmful to health, and which can be ranked somewhere between harmless and toxic substances. In the present instance poisons are considered to be those substances which are frequently harmful to health, or in certain cases may bring about death by being inhaled, ingested or by infiltration through the skin. But neither true poisons nor substances which have a harmful effect on health have been clearly defined, and it is also difficult to classify hazardous materials. The reason for the difficulty in clearly defining hazardous and harmless substances is that some substances, such as table salt, are harmless and even necessary to life when taken in small doses but may be toxic when taken in larger doses. Another common example is sugar, which can be deadly to diabetics.

Where food products have some biological activity because of some chemicals in them, these materials are considered to have a toxic effect for a toxic dose, and even when the effect is at the level thought to be effective for the purposes of medical drugs, this is generally considered to be toxic. In the case of drugs, where substances are consumed because they are effective in the treatment of particular illnesses and conditions, they may be shown to be effective in alleviating the symptoms of the person treated, but when the same dose is taken as a food, and is consumed by people who have no need of the medical effect of the substance, then although its medical effect is not harmful over a short period, if substances whose effective level borders on the toxic level are consumed over a long period, i.e. if they are substances which may be presumed possibly to have a bad effect, not only is there no clear boundary between an effective dose and the no-effect dose, but almost all chemicals which accord with the definition given above may be considered to be toxic. Food pollutants have been considered recently by the mass media, but because these were represented as existing levels in ppm or ppb, and because the emphasis was placed only on the fact that these levels exist, without any mention of the effect on human beings who have accumulated amounts at this level, this has given rise to unnecessary anxiety.

By contrast with medical drugs, which are used for the effective treatment of certain illness, and food products which are necessary to support life and maintain health, the additives in rubber and plastics used for packaging and containers or utensils, where these come into contact with food products during their preparation, processing or storage, and may be consumed along with the food, should have no effect on the human body.

3. METHODS OF EVALUATING TOXICITY (refs. 2 and 3)

The various types of toxicity tests are usually classified according to the length of the test period, but in order to ensure safety with regard to the use of the substances tested, their chemical properties and biological effect, we can classify the tests in terms of special toxicity as shown in Table 1.

In addition to investigating toxicity phenomena from a wide variety of angles, in particular from the results of tests carried out on animals, toxicity tests are necessary as the sole means of estimating the harm which can afflict a human being. All kinds of improvements are observable in the techniques and methods of assessing toxicity, owing to the rapid progress which has been made in pharmacology, toxicology and biochemistry, supplemented by examination of the real nature of toxicity, the substances causing it and the ways in which it can be represented. Table 2 shows the classifications of toxicity.

3.1 *Methods of expressing toxicity*

The abbreviations generally used for expressions of toxicity are as follows:

LD_{50} — Median Lethal Dose — dose giving 50% mortality rate (mg/kg)

LC_{50} — Least Concentration — lowest concentration of drugs resulting in 50% mortality (ppm)

TL_m — Median Tolerance Limit — concentration sufficient to cause 50% mortality of fish after keeping for 96 days (mg/l)

TLV — Threshold Limit Value — permissible concentration (dose) (ppm)

TD — Tolerated Dose — dose of drug resulting in symptoms of illness in animals (mg/kg)

TC — Tolerated Concentration — concentration of drug resulting in symptoms of illness in animals

MNL — Maximum No-effect Level

MLD — Minimum Lethal Dose

MTD — Maximum Tolerated Dose

MED — Minimum Effective Dose

ADI (PADI) — Acceptable Daily Intake — dose which can be taken daily (mg/kg) (mg/person-days)

(i) Unconditional intake zone

(ii) Conditional intake zone

Table 1 Types of toxicity tests

General toxicity	*Acute toxicity* *Short-term chronic toxicity (sub-acute toxicity)* *Long-term chronic toxicity*
Special toxicity	*Local irritation* *Allergies* *Deformities* *Effect on fertility* *Dependence (habit-forming)* *Carcinogenicity*

...tion of toxicity

...of rats ...istered ...g/kg)	Estimated lethal dose for human beings
...1–50	60 mg (1 mouthful)
...50–500	4 cc (1 teaspoonful)
...500–5,000	30 g (1 oz.)
...5,000–15,000	about 250 g
...>15,000	about 500 g
	>500 g

...tion of toxicity on the basis of

...of toxicity	LD_{50} (dose administered per kg of body weight of rat)
...high toxicity	Less than 1 mg
...toxicity	1–50 mg
...toxicity	50–500 mg
...toxicity	0.5–5 g
...toxicity	5–15 g
...non-toxic	above 15 g

...lethal doses (mg/kg) of toxins or danger-

...method of ...istering	Oral feeding	Subcut-aneous injection	Intrav-enous injection
...	<30	<20	<10
...sub-	<300	<200	<100
...drugs	>300	>200	>100

...toxicity (ref. 5)

...large doses are injected or fed into the stomach, ...abdomen of mice, rats and rabbits, and when a ...dose is discovered which causes the death of 50% ...test animals (LD_{50}) this shows the acute toxicity of ...substance. However, the LD_{50} value of a material does ...show whether there is any danger resulting from ...migration, nor does it show whether the toxic ...passed when, after a certain period of time a large ...of this substance is accumulated in the organism. ...does it show whether the substance may be car-... Acute toxicity tests have no importance in ...whether certain substances can cause ...foetal deformaties or mutations, or mental ...

The LD_{50} value represents the dose of substances (drugs, toxins etc) expressed in mg/kg or g/kg which under ...conditions results in a death rate of 50% of the ...tested. The drug is given gradually to a group of ... and the death rate (ordinate axis) is plotted ...the dose given (abscissa axis), resulting in an S-...curve. The curve is symmetrical around the 50% ...point, where the change in the amount of toxic ...has the most marked effect on the death rate. ...the LD_{50} shows a greater sensitivity than LD_{25} or LD_{75}, ...is frequently used as a quantitative indication of the ...of drugs. To express the toxic strength of drugs ... Japan we make use of the expressions normal ... strong drugs and poisonous drugs, which are

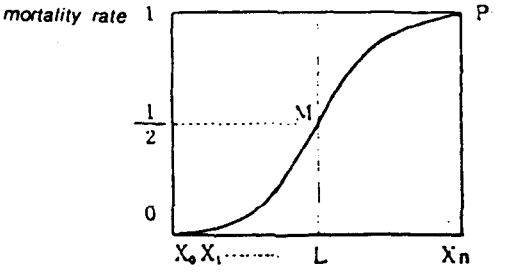

Fig. 2 Curve showing dose level vs. mortality

classified according to the value of LD_{50} when the drug is injected hypodermically into mice (see Tables 3 and 4).

The LD_{50} is found from sampling of results of tests and observations with all or non-response values measured in the organisms, and has the following properties:

1. It is the median value
2. Where the frequency distribution is symmetrical it coincides with the mean
3. Where the frequency distribution is asymmetric it coincides with the mode.
4. It is the value with the highest sensitivity.

Accordingly, since the tests require a large number of animals, small, inexpensive animals, particularly mice and rats, are most commonly used, though the use of rabbits, dogs and monkeys is also very common. In the case of mice and rats, where 50 to 100 are provided, they are divided into 4—8 groups, a group containing 10 animals (in the case or rabbits and dogs 2 to 3 form a group).

All doses are given to each group, the dose being

Table 5 Acute toxicity of ordinary substances (on rats, administered orally) (ref. 3)

Substance of chemical	Purity of substance given (%)	LD_{50} [a]
Acetic acid	100%	5.2 ml/kg
	10% aqueous solution	3.5 g/kg
Boric acid	100%	5.14 g/kg
Calcium hydroxide	100%	7.34 g/kg
Corn oil	100%	>100 ml/kg
Ethanol	100%	21.3 g/kg (sic; Transl./Ed.)
	50% aqueous solution	13.6 g/kg
Fuel oil	100%	15.4 ml/kg
Glycerol	100%	27.5 g/kg
Lard	100%	>64 g/kg
Methanol	100%	12.9 g/kg
Soap (Ivory snow)	20% aqueous solution	16 g/kg
Table salt	10% aqueous solution	4.54 kg/kg
Sorbic acid	10% aqueous solution	10.9 g/kg
Sugar	10% aqueous solution	35.4 g/kg
Sulphuric acid	50% aqueous solution	2.14 g/kg
Alcohol liquor (16% alcohol concentration)	100%	70.7 ml/kg [b]

Notes: [a] the calculation is based on a standard of 100% purity; [b] 70.7 ml/kg for alcoholic liquor corresponds to 11.3 ml of ethanol per kg

Table 6 Toxicity of monomers

Rubber	Monomer	Toxicity
Natural rubber		thrombic phlebitis, fever (sulphur-cured products)
SBR	Styrene	TLV 100 ppm, skin irritant, loss of nerve functions after 1 day exposure to a vapour concentration of 375 ppm
	Butadiene	at exposure of 8000 ppm, irritation to eyes, weakening of eyesight, coughing, nose-bleeding, drowsiness, TLV 1000 ppm
NBR	Acrylonitrile	TLV 20 ppm MLD 150 mg/kg at 20–45 min exposure to 16–100 ppm, dull headache, constriction of chest, irritation of mucous membranes in eye and nose, symptoms of discomfort and nervousness. Extreme itchiness and dermatitis. Jaundice, anaemia, lymphocytosis. The Federal Register of Nov. 1974 recommends amounts of less than 500 ppm n-dodecyl mercaptan and less than 11 ppm acrylonile monomer
CR	2-Chloro-1,3-butadiene (chloroprene)	TLV 25 ppm depressant of central nervous system, also toxic effect on liver. Also danger of absorption by skin, and of hair loss. Cancer of lung and skin with less than 1 ppm of monomer
IIR	Boron trifluoride	TLV 1 ppm A highly toxic colourless gas, severely irritating to the respiratory system
	Methyl chloride	TLV 100 ppm Anaesthetic, medium toxicity, causes damage to central nervous system, liver, kidneys. 30% mortality rate under severe exposure
EPR	Ethylene	Should not exceed 1000 ppm in general atmosphere.
	Propylene	Anaesthetic, but does not cause chronic illness. Death can occur on inhalation of high-concentration vapour. TLV not yet determined
Polyurethane rubber	Tolylene diisocyanate, diphenylmethane diisocyanate	Highly toxic substances, causing asthma and associated allergies. TLV 0.02 ppm, causes mutations. NIOSH has stipulated an exposure of 0.005 ppm 8 h/day, or 0.02 ppm for 20 min

Table 7 Acute toxicity of crosslinking or vulcanising agents

Chemical name	Acute toxicity		
	Test animals	Method of administering	LD_{50}, mg/kg
1. Benzoyl peroxide (BPO)	mice	intraperitoneal	250
2. 2,4-Dichlorobenzoyl peroxide	mice	intraperitoneal	225
3. Dicumyl peroxide (DCP)	mice	orally	4100,.15 g
4. 2,5-Bis(tert. butyloxy)-2,5-dimethylhexane	mice	intraperitoneal	2400
5. Cyclohexylamine	mice	intravenous	200
	mice	oral	710
6. Di-tert.butyl peroxide (DTBP)	mice	intraperitoneal	>6000
7. Sulphur	mice	inhalation	LC_{50} S_2Cl_2 150ppm
8. Zinc oxide	mice	inhalation	LC_{50} 2500 mg/cu.m TLV 5 mg/cu.m
9. Calcium oxide	mice	inhalation	TLV 5 mg/cu.m
10. Magnesium oxide	mice	inhalation	TLV 10 mg/cu.m

gradually increased. The examinations generally take 72 h, or in the case of slow-acting substances up to 1 week. Methods used for determining the LD_{50} are:

1. The Behrens-Karber method (mean lethal dose method or difference method)
2. The Van der Waerden method (the area method)
3. The Litchfield-Wilcoxon method (simplified version of the Miller-Tainter Probit method)
4. The up and down method (Dixon-Mood method, Brownlee's method)
5. The Gaddum method (the parabola equation method)

In addition there are the moving average method, Weil's method, the Reed-Munch method and others. One example is shown in Fig. 2.

With the area method the calculation is easy. As shown in the Figure we plot the logarithm of the dose against the mortality rate. The dose L corresponding to a mortality rate of 50% gives the sought value, LD_{50}. Ideally the mortality curve has a regular shape, and is symmetrical around the point M, but if the curve is irregular the area S enclosed by the curves OMP and OX_nP is approximately equal to the rectangular area $LX_n \times PX_n$.

13 show the acute toxicity of common monomers used in rubber (11), crosslinking vulcanisation accelerators (3, 6), antioxidants (7, 8 and 9), heavy metals (10) and other used in rubber (3, 6).

contained in zinc oxide, zinc carbonate and dithi- and other zinc-containing, f.g. fatty acid, com- lead and cadmium are detected as impurities carbonate. The JIS zinc oxides are quality- and the actual products contain only very small of impurities of Pb and trace elements; No. 1 con- and No. 3 0.13% of Pb and 0.05 of Cd. (ref. 12) is detected in the structure of tetramine accelerator.

is highly toxic in that it causes or solidifying of the protein in cellular with which it has a strong chemical affinity, about the arrest and destruction of all cell func- solution of formaldehyde, symptoms of acute such as irritation of the mucous membrane in the congestion of the pharynx and oedema of the lung When taken internally, formaldehyde causes to the oral cavity, oesophagus, stomach and small and in large quantities causes vomiting of blood, convulsions due to difficulties of respiration lysation, albuminuria, anuria and acidosis due to disorders, rapid loss of consciousness and collapse in death In contact with the skin it causes and inflammation. In terms of chronic toxicity, af- fection or skin contact it gives rise to inflammation of inflammation of the pharynx and larynx, and per- dermatitis Minimum lethal doses of formaldehyde as follows

Intravenous	*0.07 g/kg*
Subcutaneous	*0.35 g/kg*
Intravenous	*0.09 g/kg*
Subcutaneous	*0.22–0.5 g/kg*
Lymph glands	*0.8 mg/kg*
LD_{50}	*800 mg/kg*

permissible concentrations in air are as follows:

Industrial Hygiene	
legislation)	*5 ppm, 6 mg/cu.m*
factories	*1 mg/cu.m*
atmosphere	*0.035 mg/cu.m*

regards the toxicity of formaldehyde, the LD_{50} for rats be said to be 600—700 mg/kg, and we can infer a effect with 25 mg/day for a 50 kg adult. Akiyama et reported harmful effects on children who made regular of tableware which came into contact with for- but after tightening up of regulations for for- in 1966 this decreased.

formaldehyde resins give off formaldehyde most and leaching of formaldehyde from phenol- and melamine-formaldehyde resins is less but where there are surface cuts it is claimed that of formaldehyde is more noticeable). The reason is said to be that as urea resins have a lower temperature than the two other resins, without condensation some separate formaldehyde and this can be readily determined by UV Phenol is detectable in the anti-ager additive phenol.

has a caustic effect on the skin, and when it into contact with 25—50% of the skin surface is When inhaled it can damage the nervous system. concentration in air is 8.8—12.2 mg/cu.m. Lethal doses of phenol are as follows:

Dogs	*Oral*	*0.5 g/kg*
	Subcutaneous	*0.027 g/kg (toxic)*
Cats	*Subcutaneous*	*0.09 g/kg*
Rabbits	*Subcutaneous*	*0.6 g/kg*
Mice	*Subcutaneous*	*0.35–0.6 g/kg*
Frogs	*Subcutaneous*	*0.1–0.6 g/kg*
Human beings	*Oral*	*8.5–60 g/person*

Permissible concentrations of Soviet phenol in air have been fixed at 5 mg/cu.m in production plants and at 0.01 mg/cu.m in the atmosphere generally, and for containers the concentration is 0.001 mg/litre.

3.3 *Chronic toxicity (ref. 6)*

Tests are carried out involving the breeding and keeping of at least two types of animals for a period of at least two years. Rodents such as mice and rats should not be used, cats and dogs etc. being preferred. The substance being tested is fed to the animals over a period of at least three generations and with various numbers of stages of administration, of which the maximum conditions show a toxic effect, and the minimum conditions must not show any toxicity. However, the main concern of these breeding tests is to investigate changes in body weight, body condition, skin condition and composition of urine of the animals, and so every organ of the body is examined macroscopically or in sections microscopically.

At the same time, the dose level which does not cause any abnormality in the test animal is found and expressed as mg of the substance per kg of the animal, and this value is called the 'acceptable level'. A safety coefficient of 100 has to be introduced in order to apply these results to human beings. The reason for this is that human beings are assumed to have ten times the sensitivity of the animals tested, and some people have a sensitivity which is ten times as great as that of the average human being. 1/100 of the 'acceptable concentration' is the value expressing (mg. per kg of body weight) the dose which is safe for long-term intake by human beings, and the amount which can be taken per day is called the 'acceptable daily intake' (ADI). If it is assumed that a normal person's body weight is 60 kg, 60 times the ADI is referred to as the PADI. This is the term used in Holland to express the acceptable daily intake of a substance for use in packaging, and shows the amount in mg which can be taken in daily by human beings without hazard, or the amount which can be contained in 1 kg of food, though it should be noted that the highest daily intake of such goods as are necessary to life should be 1 kg.

Because of the knowledge which is already available concerning the hazards people are subjected to on coming into contact with these substances and their product-equivalents, it is by no means always necessary to carry out tests costing several hundred thousand yen on every new substance. In many cases 90-day sub-acute tests on animals are satisfactory. The tolerated dose can be established by 3-month tests on a large number of one species, rats for instance, or on two species, such as rats and dogs, with more of the materials, and examining each organ of the animals concerned. Of course these tests do not give as much information as the 2-year tests. For this reason, when applying the results of these tests to human beings, a safety coefficient of 500—2000 is used here to calculate the ADI value.

With the exception of agricultural chemicals, heavy metals and carcinogenic materials, a daily intake of less than 0.1 mg of any substance does not involve any toxicity hazard (the Frawley limiting value). Despite the substantial

safety coefficient, in Holland an even larger safety coefficient is being sought, and a lower intake of the order of 0.05 mg is being discussed. Even where the daily intake for a human being is less than 0.05—0.1 mg, there are still many cases of considerable irritation to the skin and mucous membrane, and the same thing can be said of many chemicals used in rubber production. Tables 14—17 show the long-term tolerated doses of rubber chemicals and plasticisers.

3.4 *Carcinogenicity (refs. 14, 15 and 16)*

The approach to the problem of carcinogenicity and some toxic reaction to their environments are illustrated in Tables 18-20.

The anti-ageing additives phenyl-α-naphthylamine (PAN), phenyl-β-naphthylamine (PBN) and aldol-β-napthylamine (AP) contain napthylamine as an impurity. α-Naphthylamine has long been regarded as a hazardous material which can cause cancer of the bladder. Pure α-naphthylamine is no longer used industrially, hence there is no industrial hygiene experience or information available concerning this material. However, its effect on animals has been tested, and no carcinogenic effect was observed. Industrial α-naphthylamine contains as much as 4—5% of β-naphthylamine, and is for this reason regarded as a hazardous substance, and precautionary measures are imperative. The impurities shown in Table 22 are contained in the anti-agers PAN, PBN and AP. It is clear from the literature and experience in industrial and environmental hygiene that even small amounts of pollution can result in irritation to groups of workers exposed to them. In Germany the anti-ager AP has been produced since 1926, and workers involved in its production have been examined recently. Despite the fact that these people have obviously been in contact with AP, there was no evidence of cancer of the bladder. Other carcinogenic substances are shown in Table 23.

Table 8 Acute toxicity of accelerators

Chemical name	Commercial name	Acute toxicity		
		Test animals	Method of administering	LD_{50} (mg/kg)
a. Aldehyde–amines				
1. Hexamethylenetetramine	*H*	*mice*	*hypodermic*	*MLD 450*
		rats	*hypodermic*	*MLD 200*
		marmots	*hypodermic*	*MLD 300*
		cats	*hypodermic*	*MLD 200*
b. Guanidines				
1. Diphenylguanidine	*D, DPG*	*mice*	*intraperitoneal*	*350,470*
	Vulkacit D	*rats*	*oral*	*520*
2. Diorthotolyl guanidine	*DT, DOTG*	*marmots*	*oral*	*MLD 120*
		rabbits	*oral*	*MLD 80*
3. Orthotolyldiguanide	*Vulkacit 1000*	*rats*	*oral*	*about 800*
c. Thioureas				
1. Ethylenethiourea	*NA-22*	*rats*	*oral*	*>100*
2. Dilaurylthiourea	*LUR*	*rats*	*intraperitoneal*	*>9000*
d. Thiazoles				
1. 2-Mercaptobenzothiazole	*M*	*wild rats*	*oral*	*100*
		household rats	*oral*	*500*
		mice	*oral*	*2000*
		mice	*intraperitoneal*	*437,733*
	Vulkacit Mercapto	*rats*	*oral*	*1800*
2. Dibenzothiazolyl disulphide	*DM*	*mice*	*oral*	*7000*
		rats	*intraperitoneal*	*2600,3000*
	Vulkacit DM	*rats*	*oral*	*>7000*
3. N,N-diethylthiocarbamyl-2-benzothiazolyl sulphide	*64*	*rats*	*oral*	*6000*
4. Zinc salt of 2-mercaptobenzothiazole	*Vulkacit ZM*	*rats*	*oral*	*>5000*
e. Sulphenamides				
1. N-cyclohexyl-2-benzothiazole-sulphenamide	*Vulkacit CZ*	*rats*	*oral*	*>7500*
2. N,N-diethyl-2-benzothiazole-sulphenamide	*Vulkacit AZ*	*marmots*	*oral*	*>2000*
3. N-oxydiethylene-2-benzothiazole sulphenamide	*MSA*	*rats*	*oral*	*7500–10,000*
	Vulkacit MOZ	*rats*	*oral*	*1980*
4. N-dicyclohexyl-2-benthiazole-sulphenamide	*Vulkacit DZ*	*rats*	*oral*	*>1000*
5. N-tert.butyl-2-benzothiazole-sulphenamide	*NS*	*mice*	*intraperitoneal*	*5000–7000*

continued on next page

Continued Acute toxicity of accelerators

Chemical name	Commercial name	Acute toxicity		
		Test animals	Method of administering	LD_{50} (mg/kg)
Tetramethylthiuram monosulphide	TS	mice	intraperitoneal	800
		mice	peritoneum	MLD 1
		rats	peritoneum	MLD 5
		marmots	stomach	MLD 10
		rabbits	stomach	MLD 100
		dogs	stomach	MLD 100
	Vulkacit MS	rats	oral	1150
Tetrabutylthiuram monosulphide		mice	intraperitoneal	>5000
Tetramethylthiuram disulphide	TT	rabbits	oral	210
		rats	oral	865
		mice	intraperitoneal	333
	Vulkacit Thiuram	rats	oral	1250
Tetramethylthiuram disulphide	TET	mice	intraperitoneal	967
		rabbits	oral	2050
Tetrabutylthiuram disulphide	TBT	mice	intraperitoneal	>5000
Dimethyldiphenylthiuram disulphide	Vulkacit J	rats	oral	>5000
Dipentamethylenethiuram tetrasulphide	TRA	mice	intraperitoneal	>3200
Dithiocarbamates				
Zinc dimethyldiothiocarbamate	PZ	rabbits	oral	400
		rats	oral	1400±99
	Vulkacit L	rats	oral	1400
Zinc diethyldiothiocarbamate	EZ	rabbits	oral	400
		mice	intraperitoneal	142
	Vulkacit LDA	rats	oral	>2500
Zinc di-n-butyldithiocarbamate	BZ	mice	intraperitoneal	>2500
Zinc pentamethylenedithiocarbamate	ZP	mice	intraperitoneal	260
Zinc ethylphenyldithiocarbamate	PX	mice	intraperitoneal	533

Ethylene thiourea (NA-22) has been banned from use in connection with food products in the Federal ..., 39, No.185, Sept. 23rd, 1974

Acute toxicity of anti-agers

Chemical name	Commercial name	Acute toxicity		
		Test animals	Method of administering	LD_{50} (mg/kg)
Aromatic amine derivatives				
p-Phenylenediamine derivatives				
N,N'-di-2-naphthyl-p-phenylenediamine	Agerite white	rats	oral	4500
N,N'-diphenyl-p-phenylenediamine	Agerite DPPD	rats	oral	MLD >710,000
	JZF			
N-isopropyl-N'-phenyl-p-phenylenediamine	Flexzone 3C,	rats	oral	1620
	Santoflex	rats	oral	720
		rabbits	oral	MLD >7500
	4010 NA	rats	oral	>3500
N-cyclohexyl-N'-phenyl-p-phenylenediamine	Flexzone 6H	rats	oral	2000
N-alkyl-N'-phenyl-p-phenylenediamine	Flexzone 5L	human beings	skin	Sensitiser
N,N'-bis(1-ethyl-3-methylpentyl-p-phenylenediamine	UOP 88	rats	oral	2400,900
		rabbits	hypodermic	1800
		rats	inhalation	LD_{50} 30 ppm
		marmots	inhalation	LD^{50} 37.5 ppm
N,N'-bis(1-methylheptyl)-p-phenylenediamine	UOP 288	rats	oral	bad effect on 0.1% of foetuses

continued on next page

Table 9 continued Acute toxicity of anti-agers

Chemical name	Commercial name	Acute toxicity		
		Test animals	Method of administering	LD_{50} (mg/kg)
8. N,N'-bis(1,4-dimethylpentyl)-p-phenylenediamine	Elastozone 33	rats	oral	1600
		rats	intraperitoneal	800
		mice	oral	800
		mice	intraperitoneal	400
9. N,N'-diakyl-butyl-p-phenylenediamine (sic; Transl..Ed.)	Tenamene 2	rats	oral	200–400
		marmots	intraperitoneal	10 ml/kg
(2) Keytone-amine condensates (quinolines)				
1. 2,2,4-Trimethyl-1,2-dihydroquinoline polymers	Agerite Resin D Flectol H	rabbits	oral	2000
2. 6-Ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline	Santoflex AW	rats	oral	800
3. 6-Dodecyl-2,2,4-trimethyl-1,2-dihydroquinoline	Santoflex DD	rats	oral	MLD 40000
		rabbits	percutaneous	MLD 10000
(3) Naphthylamines				
1. Phenyl-β-naphthylamine	PBN	rats	oral	>1000
2. Phenyl-α-naphthylamine	PAN	rats	oral	>1000
(4) Diphenylamine derivatives				
1. p-Isopropoxydiphenylamine	Agerite ISO	rats	oral	MLD 10000
		rabbits	oral	MLD 70000
2. Alkylated diphenylamine blends	Agerite Stalite	rabbits	oral	15 ml/kg
3. Styrenated diphenylamine	Agerite Stalite S DDA	rats	oral	>7500
b. Phenolic derivatives				
(1) Monophenols				
1. 2,6-Di-tert.butyl-4-methylphenol (butylated hydroxytoluene)	BHT	rats	oral	1700–1970
		rats	oral	8000
	KB	rats	oral	1700
2. 2,2'-Methylene-bis(4-methyl-6-nonylphenol), (alkylated bisphenol)	Nauga White	rats	oral	32700
3. Styrenated phenols	Wingstay S Agerite Spar	rats	oral	at 158,500 impedes growth
4. Alkylated phenols	Wingstay T	rats	oral	at 158,500 impedes growth
	Nevastain A	rats	oral	1700
	Nevastain B	rats	oral	20000
	KSM	rats	oral	2500
5. Alkyl-aralkyl phenol	TSP	rats	oral	2500
	DS	rats	oral	>2500
6. 2,6-Di-tert.butyl-(α-dimethylamino)-p-cresol	Ethyl Antioxidant 703	rats	oral	1030
(2) Polyphenols				
1. Hydroquinone	Tecquinol	rabbits	oral	200
		cats	oral	80
2. 2,5-Diamylhydroquinone	Santovar A	rats	oral	2000
		rabbits	oral	2000
3. Hydroquinone-monobenzyl ether	Agerite Alba	mice	intraperitoneal	>600
4. Pyrocatechol(1,2-dihydroxybenzene)		dogs	oral	130
		cats	oral	100
		rabbits	oral	200
		marmots	oral	160
(3) Bisphenols				
1. 2,2-Methylenebis(4-methyl-6-butylphenol)	Antioxidant 2246	mice	oral	>5000
	BKF	rats	oral	>2500
2. 2,2'-Methylenebis(4-methyl-6-cyclohexylphenol)	ZKF	rats	oral	>2500
3. 2,2'-Methylenebis(4-ethyl-6-butylphenol)	Antioxidant 425	rats	oral	>15000
4. 4,4'-Butylidenebis(3-methyl-6-butylphenol)	Santowhite Powder	rats	oral	MLD 17000

continued on next page

Continued Acute toxicity af anti-agers

Chemical name	Commercial name	Acute toxicity		
		Test animals	Method of administering	LD_{50} (mg/kg)
1,3,5-Trimethyl-2,4,6-tris(3,5-dibutyl-4-hydroxylbenzyl)benzene	Antioxidant 330	rats	oral	1500
Alkylated bisphenol composition	Cyanox LF	rats	oral	2470
		rats	percutaneous absorption	>50000
		rabbits	percutaneous absorption	>12600
Polybutylated bisphenol	Agerite Superlite	rats	oral	MTD 7500 ppm
Sindered bisphenol(bis(3-t-butyl-5-methyl-2-oxyphenyl(isobutane) (sic; transl./Ed.)	NKF	rats	oral	>2500
Thiobisphenols				
4,4'-Thiobis(3-methyl-6-butylphenol)	Santowhite Crystals	rats	oral	2345
		rabbits	oral	3200
4,4'-Thiobis(2-methyl-6-butylphenol)	Ethyl Antioxidant 736	rats	oral	6340
Thiobis(diamylphenol)	Santowhite L	rats	oral	MLD >20000
4-Butyl-m-cresol SCl_2 condensate	Santowhite MK	rats	oral	17500
		rabbits	percutaneous	MLD >10000
Others				
Organic thioacid (salts, esters)				
Nickel dibutyldithiocarbamate	NBC	rats	oral	17000
Phosphorous acid esters				
Phosphorous tri(nonylphenyl) ester	Polygard	rats	oral	19500
Imidazoles and thiazoles				
Zinc 2-Mercaptobenzimidazole	MB	rats	oral	1000
Miscellaneous				
Benzofuran derivatives	AFT	rats	oral	>2500
Composition unclear(anti-ozonants)	AFD	rats	oral	>2500
Composition unclear(anti-ozonants)	Produkt DS)	rats	oral	>650

Table 10 Acute toxicity of plasticisers

Plasticiser	Animals used	Method of administering	LD_{50} (g/kg)
(Phthalic ester)			
Dimethyl phthalate (DMP)	mice	intraperitoneal	1.38 (0.98–1.99)
Diethyl phthalate (DEP)	mice	intraperitoneal	2.83 (2.24–3.29)
Dibutyl phthalate (DBP)	mice	intraperitoneal	4.00 (2.94–5.45)
	rats	oral	8.0
Di-isobutyl phthalate	mice	intraperitoneal	4.50 (3.36–6.02)
Di-2-ethylhexyl phthalate (DOP)	rats	oral	30.6
Dicapryl phthalate	mice	intraperitoneal	14.19 (11.21–15.87)
Butyl phthalyl butyl glycollate	mice	oral	12.567
(Dicarboxylic acid esters)			
Di-2-ethylhexyl adipate (DOA)	marmots	oral	15
Di-isodecyl adipate	rats	oral	20.5
Dibutyl sebacate (DBS)	rats	oral	16.32 (lethal dose)
(Citric esters)			
Triethyl citrate	rats	oral	7.0
Triethyl acetyl citrate	rats	oral	7.0
(Epoxy plasticisers)			
Epoxidised soya bean oil	rats	oral	22.5
Glycidyl oleate	rats	oral	3.52
9,10-Epoxyaryl stearate	rats	oral	1.41
(Phosphoric esters)			
2-Ethylhexyl diphenyl phosphate	rabbits	oral	0.218–0.272
Tritolyl phosphate	rabbits	hypodermic	0.1
(Fatty acid esters)			
Butyl stearate	rats	oral	32
Methyl acetylricinoleate	mice	oral	34.9
Ethyl acetylricinoleate	mice	oral	1.36

Table 11 Acute toxicity of phthalic acid esters given orally to rats

Ester	LD_{50} (g/kg)
Dimethyl phthalate	6.9
Diethyl phthalate	9.5–31
Dibutyl phthalate	8–12
Di-isobutyl phthalate	15
Di-p-hexyl phthalate	29.6
Di-2-ethylhexyl phthalate	31
Di-isodecyl phthalate	64
Butylbenzyl phthalate	18
Dicyclohexyl phthalate	>40
Butyl phthalyl butyl glycollate	7

When a report was published at the end of January 1974 linking contact with vinyl chloride monomer (VCM) with the occurrence of a very rare disease of the liver (liver angiosarcoma) in employees of B.F. Goodrich Co., the question of the use of VCM became a problem again, and some emergency provisional standards were published on April 5 in the Federal Register by the Ministry of Labour, such as that in all stages of production of VCM, and of PVC from VCM, and of PVC processing, (1) the concentration of VCM to which workers were to be exposed in industrial environments was to be less than 50 ppm, and (2) where people had to work in environments where the concentration exceeded 50 ppm they were to wear protective clothing. These standards were put into effect immediately. This led to the appearance, on May 10, of a proposed standard aimed at reducing the above-mentioned standard of less than 50 ppm to a 'non-detection' (ND) level. However, on October 4, in the Federal Register, vol. 39, No. 194, p. 35890 the US Occupational Safety and Health Administration (OSHA) decided on a working environment standard of less than an average of 1 ppm over a period of 8 h, and allowed a delay of three months till the enforcement of this standard, starting from the 1st of

Table 12 Acute toxicity of other rubber ingredients

Chemical name	Commercial name	Acute toxicity		
		Test animals	Method of administering	LD_{50} (mg/kg)
a. Scorch-retarders				
1. Diphenylnitrosamine	Vulkalent A	rats	oral	about 2500
2. Phthalic anhydride	Vulkalent B	rats	oral	>2500
3. Benzoic acid	GV	rats	oral	1700
b. Peptisers				
1. Zinc salt of pentachlorothiophenol	Renacit IV	rats	oral	>2000
2. Zinc salt of pentachlorothiophenol + hemoporphorazine	Renacit	rats	oral	>2500
c. Blowing agents				
1. Benzene sulphonhydrazide	Porofor BSH 100%	rats	oral	<50
2. Dimitrosopentamethylenetetramine	Porofor DNO/F	rats	oral	>2900
3. Azodicarbonamide	Porofor ADC	rats	oral	>6800
d. Organic fillers				
1. Phenol-formaldehyde resins	Vulkadur A	rats	oral	>5000
e. Plasticiser				
1. Alkylsulphate ester of phenol	Measamoll	rats	oral	>80 ml/kg

Table 13 Toxicity of heavy metals

Harmful metals	Acute toxicity, LD_{50} mg/kg	Toxicity
Zinc	rabbits and rats, oral 2000 ($ZnSO_4$) mice, oral 57	above 700 ppm vomiting MLD 15 mg/cu.m nausea, diarrhoea, vomiting, abdominal pain and fever, and paralysis of digestive organs and mucous membrane
Lead	rats, oral 100 rabbits, oral 125 chickens, oral 450 (lead arsenate) human beings, oral 50 g/person (lead acetate) human beings, oral 40–50 g/person (lead carbonate)	MLD 0.5 mg/cu.m nausea, vomiting, convulsions, changes in blood and gums, neuritis (lead palsy), abdominal pain, distruction of central nervous system and tooth and jaw ducts
Cadmium	rabbits, oral, 70–150 ($CdCl_2$)	MLD 0.1 mg/cu.m nausea, vomiting, convulsions, irritating effect on eyes, hepatitis, jaundice, prevention of tooth growth, osteomyelitis, and anaemia
Arsenic	rats, oral 138 dogs, oral 30–70 marmots, oral 20–39 rabbits oral 14–30 chickens, oral 60–150 human beings, oral 5–50 mg/person	lethal dose 100–300 mg/person, acute constriction of throat and oesophagus, stomach pains, nausea, diarrhoea, bloody faeces, spasms due to lack of oxygen, vascular poisoning, paralysis of heart muscles

Table 13a Zinc oxide for industrial use according to JIS K 1410 French zinc oxide

Type / Constituents	Special	No. 1	No. 2	No. 3
Zinc oxide, %	>99.5	>99.5	>98.5	>99.0
Lead, %	<0.005	<0.03	<0.3	<0.3
Cadmium, %	—	—	<0.1	<0.1

American zinc oxide

Type / Constituents	No. 1	No. 2
Zinc oxide, %	>98.5	>98.0
Lead, %	<0.3	<0.8
Cadmium, %	<0.2	<0.3

JIS K 5102 Zinc oxide (cosmetics)

Constituents, %	No. 1	No. 2	No. 3
Zinc oxide	>99.5	>98.5	>99.0
Lead	<0.03	<0.3	<0.3

January 1975. The proposed European standard for working environments is 20—50 ppm averaged over 8 h, and where it is less than 25 ppm there is claimed to be very little possibility of any disorder of the liver. In the USA the Society of the Plastics Industry (SPI) rebutted the idea of introducing the level at 1 ppm, and the lawcourts ordered the standard to be left as it was at 50 ppm for the moment, but the President of the lawcourts shocked the SPI and the industry in general by introducing as a judicial precedent the new level of 1 ppm, to apply on and after the 1st of April 1975. In Japan, following an increase in the number of people suffering from high blood pressure in the hepatic portal system, which is a pre-symptom of an angiosarcoma, a committee of technical experts met to devise countermeasures against occupational cancer risks, and produced a report recommending a level of 2 ppm for workers coming into contact with VCM. The toxicity of VCM is shown in Table 23.

3.5 *Skin sensitisation (ref. 6)*

Acrolein—aromatic base condensates, tricrotonylidenetetramine, cyclohexylamine, hexamethylenetetramine and sulphur chloride have a strong corrosive and sensitising effect on the epidermis. Certain people are particularly

Table 14 Results of long-term exposure tests (ref.6)

Chemical name	Commercial name	MNL 2 years (ppm)	ADI (mg/kg)	PADI (mg/person/day)
1. Benzoic acid			5—10 (WHO)	300—600*1
2. Benzoyl peroxide			0—40 (UC)	
			40—75 (C)	
3. Saccharin			0—5 (UC)	
			5—15 (C)	
4. L-sodium glutamate			0—120 (UC)	
5. Tetramethylthiuram disuphide (TT)	Vulkacit Thiuram	48	0—0.025 (WHO)	7 (WHO)
6. Zinc dimethyldithiocarbamate (PZ)	Vulkacit L	250	0—0.125 (WHO)	7 (WHO)
7. 2-mercaptobenzothiazole (M)	Vulkacit Mercapto	120	0.075*1	4.5*1
8. 2,6-Di-tert.butyl-4-methylphenol (BTH)	KB	1000	0—0.5 (WHO)	30*1
9. Alkyl-aralkylphenol	TSP*2	250	0.04*1	2.5*1

Notes: (1) This ADI value is unsuitable for children under 1 year old, except for the fraction contained naturally in foods; (WHO): value formulated by the World Health Organisation; *1 : special assessment; *2 : 90 day feeding test (using a safety factor of 500); VC : underconditional (sic; Transl./Ed.); C : conditional

Table 15 Acceptable daily intake for human beings (mg/kg of body weight)

Name of substance	Unconditional	Conditional
Ethyl phthalyl ethyl glycollate	0—2.5	2.5—5.0
p-tert.butylphenyl salicylate	0—1.0	1.0—2.0
Di-2-ethylhexyl phthalate	0—1.0	1.0—2.0
Di-isobutyl adipate	0—2.5	2.5—5.0
Epoxidised soya bean oil	0—12.5	12.5—25.0
Acetyl tributyl citrate	0—10.0	10.0—20.0
Dibutyl sebacate	0—30.0	30.0—60.0
Dibutyl phthalate	0—1.0	1.0—2.0
Butyl stearate	0—30.0	30.0—60.0

Table 16 No-effect level of DEHP(?, DOP; Ed.)

Test animals	Feeding period (days)	No effect dose (mg/kg/day)
Rats	365	400
Rats	730	80
Dogs	98	100
Rats	90	200
Dogs	98	100
Rats	365	>60, <200
Guinea-pigs	365	about 60
Dogs	365	about 60

Table 17 No-effect level of C_6–C_9 PAE (? phthalic acid ester)

PAE	Test animals	Feeding period (days)	No effect level (% of food)	No effect level (mg/kg/day)
Dihexyl	rats	90	0.5	300
	dogs	90	1.0	200
Di-2-ethyl-hexyl	rats	730	0.4	200
	dogs	90	0.06 ml/kg/day	60
Dialkyl	79 rats	90	0.125	60
Diisononyl	rats	90	150 mg/kg/day	150
	dogs	90	0.125 (? 0.5)	25–50 (? 150–175)[a]

Note [a]: increase in the weight of the liver of males only

Table 18 Questions in connection with carcinogenicity

What is the amount which when used will give the least effect?
What is the mechanism of assimilation?
What are the products of assimilation?
Is the substance accumulated in the body?
Methods of expulsion of the substance?
How does it enter the body?

Table 19 Actions of inorganic toxins in the present-day environment

Name of substance	Location [c]	Toxicity: Estimated	Toxicity: Verified	Tendency regarding the environment
Arsenic [a]	N.T.B.	Carcinogenic		↓
Lead [a]	L.N.B.	Affects blood Affects nerves Causes mutations		↑
Cadmium [b]	N.B.	Affects kidneys High blood pressure Carcinogenic		↑

[a] natural product; [b] refined product;
[c] L = atmosphere; N = food products; T = drinking water; B = at work

Table 20 Actions of organic toxins in the present environment

Name of substance	Location [c]	Toxicity: Estimated	Toxicity: Verified	Tendency
Benzene	L.B.	Anaemia Causes mutations		
Carcinogens				
Polycylic hydrocarbons	L.N.	Carcinogenic Causes mutations		
Aromatic amines	N.B.			
Epoxy compounds	L.N.B.			
N-nitroso compounds	N			
Organic peroxides	N	Affects nerves		
Biphenyl polychlorides	N	Affects liver		

[a] L = atmosphere; N = food products; B = at work

Table 21 Impurities in anti-agers

Name of impurity	PAN	PBN	AP
α-Naphthylamine	0.5%	Not found by analysis	0.2–0.3%
β-Naphthylamine	Not found by analysis	Max 0.002%	Not found by analysis

Table 22 Types of carcinogenic substances

Name of substance \ Test subjects	Rats	Dogs	Human beings
α-Naphthylamine	Neg	C	C
Benzidine	C	C	C?
m-Tolylenediamine	C	–	Neg
Methylene bis(O-chloroanilone)	C	Neg–6 yr	?
Ethylenethiourea	C	–	?
Phenyl-β-naphthylamine	–	Neg	Neg

C = carcinogenic

Table 23 Toxicity of vinyl chloride monomer

Monomer (ppm)	Time of exposure	Result (using marmots)
400	12–20 sec	Death
200	18–55 min	Death
100	120–300 min	Marked delay in sensory perception
50	300 min	Delay in sensory perception
10	480 min	Has no narcotic effect

susceptible to the effect of some of these compounds, though this is rare and may be due to some hereditary factor. These cases are called allergic reactions (mono- or polyallergies) and can be predicted by certain methods. Care should be taken to see that the skin of such people does not come into contact with particular chemicals. There are also cases of people being hypersensitive to various natural products such as grass seed and primroses, or to foods such as strawberries or fish. If a ban were placed on the use of all chemicals connected with some observed allergy, probably very few would remain in use. One could quote, for example the derivatives tetramethylthiuram disulphide, zinc dimethyldithiocarbamate, 2-mercaptobenzothiazole, diphenylguanidine, di-o-tolylguanidine (sic; Ed./Transl.), hexamethylenetetramine, phenyl-β-naphthylamine, p-phenylenediamine. Where this type of allergic skin eruption is observed either the person's place of work should be changed or the actual materials should be replaced by others which are equally effective. For exam-

cases are quoted in the literature where N-(1,3-dimethylbutyl)-N'-phenyl-*p*-phenylenediamine was used instead of N-*iso*propyl-N'-phenyl-*p*-phenylenediamine, though the sensitising effect of isopropyl compounds such as this has probably been exaggerated.

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