Handbook of Toxic Properties of Monomers and Additives

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Dr. Sheftel received his higher education (M.D.) at the Kiev Medical Institute, Ukraine. After having obtained a Ph.D. in 1966, he was a senior researcher and team manager at the All-Union Research Institute of Hygiene and Toxicology of Pesticides, Polymers and Plastic Materials (Kiev, Ukraine). He performed research work aimed at the development of the modern toxicology of plastics as a new branch of applied toxicology.

By 1978 he earned his third degree (D.Sc.) at the Sysin Research Institute of Environmental Hygiene (Moscow) in the Academy of Medical Sciences of the USSR.

Dr. Sheftel has published 12 monographs and over 50 scientific papers, mainly related to the toxicological evaluation of food- and water-contact materials and contaminants, the methodology of regulatory process in this field, and other actual problems of general and applied toxicology. In 1990 Dr. Sheftel emigrated to Israel. At present his work in the Ministry of Health is concerned mainly with the problems of drinking water safety. Simultaneously he is involved in research work targeting the development of a toxicity prediction system for carcinogens, developmental toxicants, etc., on the basis of advanced software for building quantitative structure–activity relationship models.

PREFACE

Plastics or ***polymeric materials*** (PM) appear to be an important source of chemical contamination of food and environment, along with industrial wastes and pesticides. For the last several decades, the safety assessment of plastics intended for use in contact with foodstuffs or drinking water continues to present a serious challenge for industry and regulatory agencies.

Toxicology of plastics studies a potential hazard of polymeric materials and their ingredients for human health and develops recommendations for production and safe use of such materials.

Since it is a comparatively new and insufficiently investigated branch of applied toxicology, the experimental data obtained in this field hitherto have not been collected and generalized. Incomplete and fragmentary information on the subject could be found in the following sources: Patty's *Industrial Hygiene and Toxicology,* 3rd ed. (1982); *Practical Toxicology of Plastics,* CRC Press, 1968, and *Les Matieres Plastiques dans l'Industrie Alimentaire,* Paris, 1972 (in French), by R. Lefaux; *Industrial Hazards of Plastics and Synthetic Elastomers,* by J. Jarvisalo, P. Pkaffli, and H. Vainio, Eds., Alan R. Liss, Inc. (1984). Unfortunately all of these books are already out of date.

This handbook is an attempt to provide comprehensive information on the toxic effects of plastics ingredients that enter the body mainly by the oral route and thus it may serve as a sort of encyclopedia for specialists and practitioners in their field. Basic toxicological and other scientific data necessary to identify, characterize, measure, and predict hazards of plastic-like materials use have been assembled from the scientific literature and from regulatory national and international documents.

The contents of this handbook factually overstep the limits of toxicology of plastics because they comprise information concerning many of the widespread food and water contaminants: heavy metals, solvents, monomers, plasticizers, etc. Because toxic properties of PM depend on toxic properties of the substances released by them, this book will be of use when assessing toxic properties not only of the existing plastics but also of future materials containing ingredients that have already undergone toxicological evaluation.

The handbook includes the thoroughly reviewed American and European toxicology literature, as well as the screened Russian toxicology data, unknown in the West but reasonably fit to interpretation. Since the toxic properties of PM are determined by the toxic properties of the substances released by them, toxic hazard assessment of ingredients migrating into food and water is the essential part either of new material development or of the regulatory decision-making process.

It should be borne in mind that assessment of toxic potential is an exclusively complicated task even for those who have many years of experience in toxicology testing. Such assessment requires examining and scrutinizing of complex data that describe the toxicology of a substance, selecting the appropriate valid information from often conflicting or incomplete data, and arriving at a conclusion on the relevance of the information to human health risk.

For these and other reasons, it has not been possible to assess exactly a relative validity either of data obtained before GLP implementation or of "Russian" toxicology data. On the other hand, a toxicology profile will be incomplete today if only findings of the last decade are taken into account. Russian toxicology developed separately from that of the West. Since much data collected in Russia is unique, it cannot be ignored, even if it does not completely conform to GLP requirements. In every case, references should enable easy identification of the place and year of each research cited.

The following remarks concerning presentation of the data in this handbook are to be made:

1. For each chemical, the following data are provided when available:

   - Substance Prime Name
   - Synonyms
   - CAS Number
   - Properties (sometimes Composition)
   - Applications and Exposure (sometimes Migration Levels)
   - Acute Toxicity
   - Repeated Exposure
   - Short-term Toxicity

- Long-term Toxicity
- Immunotoxicity or Allergenic Effect
- Reproductive Toxicity (Embryotoxicity, Teratogenicity, and Gonadotoxicity)
- Genotoxicity
- Carcinogenicity (including IARC, USEPA and NTP Cancer Classification)
- Chemobiokinetics
- Standards, Guidelines, Regulations, Recommendations
- References

2. The oral route of administration is intended throughout the book unless otherwise specified. In the absence of oral toxicity data, information from inhalation or dermal toxicity studies, as well as from administration via i/p, i/v, or other routes, is presented.
3. Description of the common toxic effects is subdivided into acute, repeated, short-term, and long-term (chronic) toxicity: **acute toxicity** refers to the result of a single oral exposure; **repeated exposure** refers to a length of exposure being about 2 weeks to 2 months; **short-term toxicity** refers to a period of treatment not less than 3 to 4 months; **long-term toxicity** refers to a length of exposure not less than 6 months.
4. A quantitative assessment of functional accumulation is given. **Coefficient of accumulation** (on the lethal level) has been determined by one of the following three methods: the method of Yu. S. Kagan and V. V. Stankevich (designated as "by Kagan") stipulates administration of the agent to experimental animals at equal daily doses of 1/5 to 1/50 LD_{50} for 2 to 4 months; the method of R. K. Lim, et al. (designated as "by Lim") stipulates administration of the substance at gradually increasing doses, beginning with 1/10 LD_{50} for no more than 4 weeks; the method of S. N. Cherkinsky, et al. (designated as "by Cherkinsky") stipulates administration of 1/5 LD_{50} for 20 days.
5. Data on certain long-term or "delayed" effects, in particular carcinogenicity, may not present appropriate information about the safe levels. These data are usually obtained at high dose-levels, and recommendations for carcinogenicity evaluation have been computed from hypothetical mathematical models that cannot be verified experimentally.
6. There are three most acknowledged **carcinogenicity classifications:** IARC, USEPA and NTP. All substances tested could be subdivided according to **IARC weight of evidence** for carcinogenicity: **1**—*Human carcinogens;* **2A**—*Probable carcinogens;* **2B**—*Possible carcinogens;* **3**—*Not classified;* **4**—*Probably not carcinogenic to humans.* According to **USEPA weight of evidence** for carcinogenicity the classification is as follows: **A**—*Human carcinogens;* **B1** and **B2**—*Probable human carcinogens;* **C**—*Possible human carcinogens;* **D**—*Not classified;* **E**—*No evidence of carcinogenicity in humans.* **NTP categorization** according to the weight of the experimental evidence is presented by the following groups: **CE**—*Clear evidence of carcinogenic activity;* **SE**—*Some evidence of carcinogenic activity;* **EE**—*Equivocal evidence of carcinogenic activity;* **NE**—*No evidence of carcinogenic activity;* **IS**—*Inadequate study of carcinogenic activity.* Earlier NTP designations are as follows: **P**—*Positive;* **E**—*Equivocal;* **N**—*Negative.* Designations of this categorization are displayed in the following order: *Male Rats—Female Rats—Male Mice—Female Mice.* Absence of the data is designated as **XX.** Rodent carcinogens with significantly elevated tumor rate at some dose(s) below MTD are marked with * (according to J. K. Haseman and A. Lockhart, 1993).
7. Within chapters, ingredients are placed in the English alphabetical order of their prime names, ignoring special characters such as Greek letters or numerals. Toxicity data are transformed into a special, newly developed format to facilitate the use of available toxicology information to evaluate potential migration levels of plastic ingredients into food or drinking water.
8. WHO, EEC, U.S., and some other available national standards, guidelines, and recommendations, taken from the following sources, are presented: "WHO Guidelines for Drinking-Water Quality," November, 1992; "Council Directive of 15 July 1980," *Official Journal of European Communities,* 30, 8, August 1980; "Drinking Water Regulations and Health Advisories" by USEPA, 1991; Commission Directive 90/128/EEC of 23 February 1990 relating to plastics materials and articles intended to come in contact with foodstuffs," *Official Journal of European Communities,* 33(L75), 19, 1990; Code of Federal Regulations, Food and Drugs, 21 CFR Part 175–179, 1993; List of Maximum Allowable Concentrations set by Ministry of Health, the

USSR, Appendix 2, Sanitary Rules and Standards, No. 4630–88, 1988. References to USFDA are cited according to CFR.

9. Definitions of abbreviations:

ADI—Acceptable Daily Intake
CFR—U.S. Code of Federal Regulations
DWEL—Drinking Water Equivalent Level
ET_{50}—Median time from ingestion up to death of animals after LD_{50} administration
GLP—Good Laboratory Practice
GRAS—Generally Recognized As Safe
K_{acc}—Coefficient of Accumulation
LC_i—Lethal Concentration (subscript indicates percentage of mortality)
LD_i—Lethal Dose (subscript indicates percentage of mortality)
LOAEL—Lowest-Observed-Adverse-Effect-Level
LOEL—Lowest-Observed-Effect-Level
MAC—Maximum Allowable Concentration in water bodies
MCL—Maximum Contaminant Level in drinking water
MCLG—Maximum Contaminant Level Goal in drinking water
MPC—Maximum Permissible Concentration in food
MTD—Maximum Tolerable Dose
n/m—not monitored
NOAEL—No-Observed-Adverse-Effect-Level
NOEL—No-Observed-Effect-Level
NTP—U.S. National Toxicology Program
organolept.—organoleptic criterion
PML—Permissible Migration Level to food or water
PTWI—Provisional Tolerable Weekly Intake
QM—Maximum Permitted Quantity of the residual substance in the material or article
RfD—Reference Dose
RTECS—Registry of Toxic Effects of Chemical Substances
SML—Specific Migration Limit in food or food simulant
TDI—Tolerable Daily Intake
UF—Uncertainty factor
ALT—alanine aminotransferase
AST—aspartate aminotransferase
BW—body weight
CA—chromosome aberrations
CNS—central nervous system
DLM—dominant lethal mutations
DNA—deoxyribonucleic acid
ECG—electrocardiogram
EEG—electroencephalogram
GI—gastrointestinal
Hb—hemoglobin
LDH—lactate dehydrogenase
MetHb—methemoglobin
NS—nervous system
RNA—ribonucleic acid
STI—summation threshold index
SCE—sister chromatid exchanges
i/g—intragastric administration
i/m—intramuscular injection
i/p—intraperitoneal injection
i/v—intravenous injection
s/c—subcutaneous injection
ppm—parts per million
ppb—parts per billion

10. Reference numbers related to the most repeatedly used literature sources:

- 01—Alexander, H. C., McCarty, W. A., and Bartlett, E. A., Aqueous odour and taste threshold values of industrial chemicals, *J. Am. Water Works Assoc.*, 74, 595, 1982.
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- 04—Lefaux, R., *Chimie et Toxicologie des Matieres Plastiques*, Paris, 1964 (in French).
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- 010—*Identification and Treatment of Tastes and Odors in Drinking Water*, Mallevialle, J. and Suffet, I. H., Eds., AWWA Research Foundation, Lyonnaise des Eaux-Dumez, 1987, p. 292.

This handbook is intended for specialists in industry as well as for health care providers, legislators, regulators, scientists, and practitioners of occupational and environmental medicine, various national and international agencies and organizations, national and local governmental authorities and consumer associations, movements such as Greenpeace, etc.

Application of the appropriate data base should present complete and necessary information for many of those concerned with research, application, and legislation relevant to toxic hazards of packaging materials and food-contact coatings and articles. The author has made every effort to ensure that the information presented in this handbook is accurate and up-to-date. Nevertheless, despite reasonable screening and evaluation of presented data, inclusion herein does not imply endorsement of the cited literature. No claims of assurance or liability for the misaccuracy of information presented are assumed, either by the author or the publisher. Final evaluation of the references included is the responsibility of the readers.

Victor O. Sheftel, M.D., Ph.D., D.Sc.
Jerusalem, 1994

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INTRODUCTION:

HARMFUL SUBSTANCES IN PLASTICS

As it stands today, not only at the production stage but also in everyday living, it is unlikely that the population could avoid coming into contact with plastics. Approximately 70 to 80% of food is packaged in various *polymeric materials* (PM).

Unfortunately, PM appear to be a potential source of the release of chemicals into the environment; they may have a variety of effects on human health through water, air, or skin contamination. The principal harmful factor associated with the use of PM remains the possible contamination of food.

The absence of acute poisonings with fatal outcomes does not prove the safety of synthetic packaging materials. Nevertheless, it must be remembered that we do not completely realize the real contribution of PM to the actual contamination of foodstuffs.

It is true that PM ingredients do not act like pesticides (or a variety of other highly bioactive substances), and one can hardly expect immediate and pronounced clinical manifestations of their toxic action. The occurrence of acute toxicity due to plastics materials used in contact with food and drinking water is most unlikely, since only trace quantities of toxic substances are likely to migrate. PM may produce chronic effects as the result of repeated ingestion of a number of small doses, each in itself insufficient to cause an immediate acute reaction but in the long term having a cumulative toxic effect. Thus, PM and other widely used chemicals have brought to light the problem of the protracted action of low concentrations of chemicals upon human health.

PM are likely to be a *depot* of organic (sometimes also inorganic) compounds which, during the "life-span", are discharged into the environment, polluting various contact media, such as food, water, air, skin surface, etc. (Whenever food or drinks contact a solid surface, the resulting food contaminants could be called *migrants*). Since PM ingredients have the potential to migrate from the plastics packaging or wrapping materials into the food in measurable amounts and thereby become the *indirect food additives,* these migrants have to be appropriately regulated (Title 21 of the *Code of Federal Regulations,* part 175–179). U.S. CFR lays out general safety requirements for all *indirect food additives* covering the safe use of food-contact PM.

Under the *Food, Drug, and Cosmetic Act,* an industry must show that a new PM having indirect contact with food such as packaging material or can coating material, is safe for the intended use. Appropriate toxicology information, along with the results of animal toxicity tests, is submitted to the *Food and Drug Administration* (FDA) for review as a part of a *Food Additive Petition.*

Thus, a toxicological evaluation of extractable contaminants is essential in selecting materials for use in contact with food and/or drinking water for verifying that even if migration occurs, no known toxic hazard will exist to the consumer.

It is known that food contact applications are numerous and include the use of plastics, cellulose, paper, aluminum foil, glass, rubber, printing inks, and coatings. PM are widely used in particular in contact with foodstuffs, namely, in food processing equipment, food utensils, and as food packaging.

PM are manufactured by polymerization or polycondensation of one or more monomers and/or other starting substances. As basic polymers the following compounds are most widely used (21 CFR):

- Vinyl resinous substances (polyvinyl acetate, polyvinyl alcohol, polyvinyl butyral, polyvinyl chloride, polyvinyl formal, polyvinylidene chloride, polyvinyl pyrrolidone, polyvinyl stearate, a number of polyvinyl chloride copolymers);
- Styrene polymers (polystyrene α-methyl styrene polymer, styrene copolymers with acrylonitrile and α-methyl styrene);
- Polyethylene and its copolymers;
- Polypropylene and its copolymers;
- Acrylics and their copolymers;
- Elastomers (butadiene-acrylonitrile copolymer, butadiene-acrylonitrile-styrene copolymer, butadiene-styrene copolymer, butyl rubber, chlorinated rubber, 2-chloro-1,3-butadiene/neoprene, natural rubber, polyisobutylene, rubber hydrochloride, styrene-isobutylene copolymer).

In the preparation of PM, numerous additives are used, and the nature of these is dependent on the type of polymer being produced. Examples of the additives that may be used are *plasticizers, antioxidants, catalysts, suspension and emulsifying agents, stabilizers, and polymerization inhibitors, pigments, fillers,* etc. These additives are bound either chemically or physically into the polymer and may be present in their original or altered form. In addition, the polymerization process may leave trace quantities of residual monomer or low-molecular-mass polymer in the PM. It is therefore necessary to specify the purity of the polymer to be used in the preparation of PM intended for food and/or drinking water contact use.

Subsequently, PM contain a spectrum of polymers of different molecular mass, products of side reactions, and residues of all the auxiliary chemicals.

The migration potency of PM is predominantly determined by the availability of unpolymerized monomers, residues of catalysts, transformation products of other starting ingredients, and destruction products (about 3000 PM components are listed by the EC Commission as conceivable migrants). The structure of PM could be changed through time as a result of destruction and ageing processes and of leaching or evaporation of PM ingredients or of their interaction product.

All additives are liable to break down during processing; some, such as antioxidants, are intended to do so to fulfill their function. A number of PM release not only additives into the environment but also monomers that could be present in PM as residues or have appeared as a result of destructive processes. As a matter of fact, PM appears to be a complicated and mobile system that is more or less stable, depending on its age, production technology, and conditions of actual use.

Potential migrants encompass a large group of substances of differing molecular mass and physical properties. In some cases it is impossible to determine accurate amounts of ingredients migrating from PM into contact media. Migration levels can be affected considerably by destruction processes and ageing of plastics, by the presence of unbound low-molecular compounds. The extent to which migration occurs will depend upon such factors as the contact area, the rate of transfer, the type of PM, the temperature, and the contact time. The migration of substances from PM into food is also related to the type of food packaged in PM. Alcoholic beverages and edible fats and oils will extract substances more readily than dry foods such as cereals.

The *high-molecular mass polymer* itself does not pose a toxic hazard, being inert and essentially insoluble in food. *Monomers* are very reactive and biologically aggressive. Some of them have been shown to cause allergic effects, to damage the liver and reproductive functions, and to induce carcinogenicity.

Plasticizers are used to assist processing and impart flexibility to plastics. Plasticizers can be present in food packaging materials in significant amounts and have the potential to migrate into food.

In the food packaging and food processing industries, the major plasticizers used are *di(2-ethylhexyl) adipate* [DEHA], polymeric species, *epoxidized soybean oil* [ESBO], and *acetyl tributyl citrate* [ATBC] in packaging films and *di(-2ethylhexyl) phthalate* [DEHP], *diisodecyl phthalate,* and *diisooctyl phthalate* in closure seals for containers.

Those currently used in polyvinyl chloride [PVC] include *phthalates, phosphates, aliphatic dibasic acid esters,* and *polyesters.* The plasticizers most widely used in PVC for food contact applications are DEHA, DEHP, and polymeric species. Different plastics may contain markedly different levels of phthalate plasticizers. ATBC is commonly used in vinylidene chloride copolymers, ESBO is also used in polyvinyl chloride and vinylidene chloride copolymer films.

The main function of *stabilizers* is to prevent destruction of PM. *Antioxidants* are introduced to avoid undesirable oxidation. Stabilizers and antioxidants are not bound to polymeric macromolecules and could be leached easily into contact liquid media. Thermal stabilizers contribute to food contamination with their own residues.

Catalysts and *hardeners* usually occur in the finished product. Catalysts of polycondensation (e.g., alkali and acids) seem to be less aggressive in comparison with catalysts used in polymerization.

A number of PM ingredients listed for use in the U.S. and EEC regulations have been shown to migrate into the foodstuffs and simulant media under ordinary conditions at significant concentrations. Modern chromatography techniques, including capillary gas chromatography and high-performance liquid chromatography (HPLC), together with other highly-selective detectors (FID,

electron capture, nitrogen-phosphorus, MS for GC, UV, electrochemical, fluorescent, mass spectrometry for HPLC) allow the separation, identification, and precise determination of the majority of toxic substances migrating from plastics to contact media at the levels required for safety evaluation.

Advances in analytical chemistry have made it possible in many cases to decode the complex set of chemicals released from PM. Analytical chemistry has gradually become a method of routinely monitoring the safety properties of plastics that can estimate or measure directly PM contamination.

In order to prevent or eliminate the risk of a health hazard to a population exposed to PM, U.S. CFR lays out general safety requirements for all indirect food additives covering the safe use of food- and water-contact PM. It regulates the use of such materials and articles in contact with food in accordance with prescribed conditions. EEC regulations of plastic materials and articles intended to come in contact with foodstuffs in some cases prescribe an overall migration limit in food and food simulants and maximum permitted quantities of the 'residual' substance in the plastic materials and articles. These regulations include provisions applicable when checking migration limits and a positive list of monomers and other starting substances that may be used in the manufacture of materials and articles intended to come into contact with foodstuffs.

Neither the CFR nor the EEC regulations explain why they are publishing the long records of PM ingredients. The positive lists produce a certain unfavorable effect, creating the illusion that the PM composition is safe. This opinion, shared by many, is erroneous. Sometimes a legislator must admit reluctantly that "such a list *would offer no tangible benefit* (bolded by the author—V. S.) in terms of safeguarding human health" (Commission Directive 90/128/EEC). Then what benefit can they offer? Positive lists neither contribute to the problem nor help with the solution.

Some approaches, based on an artificial hypothesis aimed to accept a level of toxicological insignificance, have been suggested in order to avoid toxicity testing of all migrants that might be present (the *overall migration test* and the so-called *threshold of regulation*). Unfortunately, so far there is little scope for such approaches since each such recommendation needs to have a firm experimental base.

Successful regulation of PM seems to be possible with the help of the newest analytical methods and achievements of modern experimental and regulatory toxicology. A correct strategy in toxicology of plastics comprises precise chemical analysis of potential contamination of food, water, or simulant media under specified conditions. Obtained in this way, analytical results must be compared with available toxicology data and safety standards.

In the author's opinion (and those who have labored long in the area will notice this), this handbook provides an opportunity to make an advancement in the regulatory toxicology of plastics, specifically to implement the modern toxicology approach instead of the application of an out-of-date limit of total extractives and positive lists.

Chapter 1

MONOMERS

ACETALDEHYDE (CAS No 75–07–0)

Synonyms. Acetic aldehyde; Ethanal; Ethylaldehyde.

Properties. Colorless liquid with a pungent odor of rotten apples. Readily miscible with water and alcohol. Odor perception threshold is reported to be 0.034 mg/l,[02] taste perception threshold is 0.21 mg/l.

Applications and Exposure. Used in the production of synthetic rubbers, alkyd resins, and epoxy compounds. A. occurs in common dietary components such as vegetables, fruits, and beverages, and in tobacco smoke. It is a food additive.

Acute Toxicity. LD_{50} is 1.93 g/kg BW for rats,[1] and 1.2 g/kg BW for mice. The treated animals displayed adynamia and labored respiration, followed by convulsions. Death occurs within 3 to 10 min after administration.

Repeated Exposure revealed very low accumulation of A. because of its rapid decomposition in the body (7 to 8 mg/min in rabbits).[2] Rats received the doses of 25 mg/kg, 125 mg/kg, and 675 mg/kg BW via their drinking water over a period of 4 weeks. Food and liquid intake was decreased in the top-dose group. Hyperkeratosis of the forestomach in the top-dosed rats was the only adverse effect observed. The NOAEL of 125 mg/kg BW was identified in this study.[3]

Long-term Toxicity. Rats were dosed by gavage with 10 mg/kg and 100 mg/kg BW for 6 months. The treatment affected CNS functions and increased arterial pressure.

Reproductive Toxicity. Rats were given A. on days 10 to 12 of gestation. *Embryotoxic* effects comprised a great number of fetal resorptions, edema, microcephaly, hemorrhaging, retardation of fetal growth, and other lesions, including skeletal abnormalities. The treatment resulted in reduced placenta weights and umbilical cord length.[4] Inhalation exposure to 5 mg A./m^3 produced embryotoxic effect in rats. Morphology changes in the placenta have also been reported.[5]

Genotoxicity. No data are reported on the genetic and related effects of A. in humans. However, it is capable of inducing gene mutations at the *hprt* locus in human cells.[6] A. is a well-known clastogen and SCE inducer in cultured human and hamster cells.[7] It caused DNA cross-links and CA in human cells *in vitro.* It increased the incidence of SCE in bone marrow cells of mice and hamsters *in vivo,* induced CA in rat embryos exposed *in vivo* and micronuclei in cultured rodent cells (IARC 36–101).

Carcinogenicity. Inhalation exposure increased the incidence of GI tract tumors and carcinomas of the nasal cavity in rats and of the larynx in hamsters.[8] ***Carcinogenicity classification.*** IARC: Group 2B.

Chemobiokinetics. A. is absorbed and metabolized to **acetic acid** by NAD-dependent aldehyde dehydrogenase.[9] According to Casier and Polet (1959), A. is likely to play a role in the acetylation of coenzyme A and in subsequent synthesis of cholesterol and fatty acids. Urinary excretion appeared to be nonexistent.

Regulations. USFDA (1993) regulates A. as a direct food additive. It is considered to be GRAS for its intended use as a synthetic flavoring substance and adjuvant. A. is also approved for use as a component of phenolic resins in molded articles intended for repeated use in contact with nonacid food (pH above 5).

Standards. Russia (1988). MAC: 0.2 mg/l (organolept., taste).

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ACETONITRILE (CAS No 75–05–8)

Synonyms. Acetic acid nitrile; Cyanomethane; Ethanenitrile; Ethylnitrile; Methanecarbonitrile; Methylcyanide.

Properties. Colorless liquid with an ether-like odor. In water solution, A. is hydrolyzed to form **acetamide** and **acetic acid.** May be reduced to **ethyl amine.** Readily miscible with water and alcohol. Odor perception threshold is 2.4 mg/l (Rubinsky, 1969). According to other data, odor perception threshold is 0.75 mg/l at 60°C. However, odor perception threshold of 300 mg/l is also reported.[02]

Applications. A monomer and a high-polarity organic solvent. Used also in consumer goods such as cosmetics and in various chemical industries and laboratories.

Acute Toxicity. LD_{50} is 3.8 to 3.9 g/kg BW in rats, 0.2 to 0.33 g/kg BW in mice, and 0.14 to 0.35 g/kg BW in guinea pigs (Rubinsky). According to Hashimoto, LD_{50} is 170 to 520 mg/kg BW in mice, which are shown to be among the most susceptible animals to A.[1] Rats exhibited different age sensitivity to acute poisoning; in young animals (BW up to 50 g), LD_{50} was 200 mg/kg BW, while in adult rats (80 to 100 g), it was 3900 mg/kg BW, and in old animals (300 to 400 g), it was 4400 mg/kg BW.[2] Poisoning was accompanied by adynamia or agitation, coordination disorder, convulsions, dyspnea, depression of reflexes, hypothermia, etc. Lung emphysema was found to develop in 3 h after administration of A. Death occurs as a result of respiratory arrest.

Repeated Exposure failed to reveal cumulative properties. Guinea pigs were dosed by gavage with 1/5 and 1/20 LD_{50} for 75 d. The treatment resulted in decreased CO_2 production, reticulocytosis, leukocytosis, and increased content of ascorbic acid in the liver, kidneys, and adrenal glands.[1] Gross pathology examination revealed dystrophic changes in the viscera and reduced spleen relative weights.

Long-term Toxicity. In a 6-month study, guinea pigs were exposed to the oral doses of 0.7 and 3.5 mg/kg BW. The treatment with the higher dose caused reduced catalase activity, increased relative weights of the adrenals, and elevated ascorbic acid levels in the liver and spleen. Histological examination revealed moderate dystrophic changes in the visceral organs (Rubinsky).

Reproductive Toxicity. ***Embryotoxicity.*** Sprague-Dawley rats were administered the doses of 125 to 175 mg/kg BW on days 6 to 19 of gestation. Maternal toxicity and embryotoxicity effects were observed at the high dose-level.[3] ***Teratogenicity.*** Inhalation by pregnant animals may produce malformations in the offspring (axial skeletal disorders) at maternal toxic levels. Significant teratogenic effect (exencephalia, medullary hernias, fusion of the ribs) and increased embryolethality were found after ingestion of 100 to 400 mg A./kg BW on day 8 of gestation. The treatment produced a reduction in BW of fetuses. According to Willhite,[4] these malformations were likely to occur because of the release of CN^- during A. metabolism. However, no teratogenic effect had been observed in the study.[3]

Genotoxicity. A. is not mutagenic in the standard test using *Salmonella typhimurium.*

Chemobiokinetics. A. is readily absorbed after ingestion. Cytochrome P-450 IIE1 is a probable catalyst in oxidation of AN to **cyanide** by microsomes.[5] Freeman and Hayes[6] believe the metabolism of A. occurs by cytochrome P-450-dependent pathway and not by a nucleophilic substitution reaction with glutathione. The toxic effects are attributable to the metabolic release of cyanide, but the symptoms of poisoning may be delayed due to slow hepatic metabolism.

Standards. Russia (1988). MAC: 0.7 mg/l (organolept., odor).

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ACROLEIN (CAS No 107–02–8)

Synonyms. Acraldehyde; Acrylaldehyde; Allyl aldehyde; Aqualin; 2-Propenal; 2-Propen-1-on.

Properties. Colorless, volatile, transparent liquid with a pungent odor. A. is fairly soluble in water: 200 g/l at 25°C,[02] and in organic solvents (ethanol, diethyl ether, etc.). Odor perception threshold is reported to be 0.2 mg/l[1] or 0.11 mg/l.[02]

Applications and Exposure. A. is an intermediate in the production of polymers and copolymers of acrylic acid and acrylonitrile, and cycloaliphatic epoxy resins. The product of degradation of synthetic polymers. A. could be detected in cigarette smoke and in volatile components of some foods.

Acute Toxicity. LD_{50} values in Wistar rats, mice, and rabbits are 39 to 56 mg/kg, 28 mg/kg, and 7 mg/kg BW, respectively (IARC 36–143).[2,3] However, LD_{95} for Charles River rats is 11.2 mg/kg BW, and five out of ten rats died following administration of a single oral dose of 10 mg/kg by gavage.[4]

Repeated Exposure. Mice were dosed with 1.5 mg/kg BW for a month. The treatment caused decrease in the food consumption and morphological changes in the liver and kidneys. The NOEL appeared to be 0.17 mg/kg BW.[1]

Long-term Toxicity. Chronic human exposure is unlikely due to severe irritating properties of A.[5] In a 6-month study,[1] disorders of the kidney (protein in the urine) and liver functions (shortening of the prothrombin time) were found in rats. Histological examination revealed pneumonia and reduced relative liver weights. In a 1-year study, beagle dogs received 0.1, 0.5, and 1.5 mg A./kg BW (as 0.1% aqueous solution in gelatin capsules). After 4 weeks the highest dose was increased to 2 mg A./kg. The major test effect was frequent vomiting after dosing. This was considered to be an adaptive effect. Serum albumin, calcium, and total protein values were found to be depressed only in high-dosed animals.[6]

Reproductive Toxicity. A. has not been found to be a selective reproductive toxin in the rat. It produced toxic effects down to a dose-level of 3 mg/kg BW.[7] ***Embryotoxicity.*** A. is a metabolite of **cyclophosphamide,** which is a known embryotoxic agent. A. produces the embryotoxic effect in rats, inhibiting fetal growth[8] but only at maternal toxicity level. The data on the toxic effect of A. on chick embryos are contradictory.[9,10] ***Teratogenicity.*** There is no solid evidence that A. produces fetal malformations. Schmidt et al. found no teratogenic activity in Sprague-Dawley rats.[11] A. was not found to be a developmental toxicant or teratogen in New Zealand white rabbits at doses not toxic to the dams (up to 2 mg/kg BW). The bigger doses (4 and 6 mg/kg BW) produced a high incidence of maternal mortality, spontaneous abortions, resorptions, and gastric ulcerations.[12]

Genotoxicity. *Humans.* There are no data available on the genetic and related effects. *Animals.* Assays on mutagenic potential revealed conflicting results. A. is unlikely to be a direct-acting mutagen.[5] It is negative in *Salmonella* mutagenicity bioassay (NTP–92) and does not induce DLM in mice but causes SCE in Chinese hamster ovary cells *in vitro* and is found to be mutagenic to bacteria (IARC 19–479; IARC 36–133).

Carcinogenicity. *Humans.* There is no evidence that A. is a human carcinogen. *Animals.* In a 104-week study, Fisher 344 rats were exposed to A. in their drinking water at a concentration of 625 ppm. No decrease in survival or increase in tumor incidence was reported. Out of 25 female rats, 5 developed adrenal cortical adenomas; 2 out of 20 rats had neoplastic nodules in the adrenal cortex. The authors did not consider the study to be a definitive carcinogenicity bioassay.[3] Parent et al. have revised the tissues from this study and found no proof of A. carcinogenicity.[14] Sprague-Dawley rats received 10 mg A./l in their drinking water for 102 weeks (equivalent to 0.05 to 2.5 mg/kg BW). The only effect was consistent depression of creatinine phosphokinase levels. No microscopic lesions in the treated rats, whether neoplastic or nonneoplastic, were noted.[14] In other chronic studies,[14] A. was given by gavage to Sprague-Dawley rats and CD-1 mice. The treatment did not produce carcinogenic response. In addition, the authors failed to observe any significant systemic effect other than increased mortality and retardation of BW gain. ***Carcinogenicity classification.*** IARC: Group 3.

Chemobiokinetics. After ingestion, A. is found to be readily absorbed in the GI tract of experimental animals. Its transport throughout the body is very low. Being a highly reactive compound, it reacts with the substances present in the tissues at the site of the contact. A. can combine with glutathione. It inhibits metabolism of xenobiotics. A. is likely to be converted into **acrylic acid.**

Standards. Russia (1988). MAC: 0.01 mg/l.

Regulations. USFDA (1993) approved the use of A. (1) as an ingredient of resinous and polymeric coatings for polyolefin films to be safely used as a food-contact surface and subject to certain limitations, (2) as a slimicide in the manufacture of paper and paperboard products to contact with food and (3) as an etherifying agent in the manufacture of food additives or of ''modified food starch'' in an amount not exceeding that reasonably required to reach the intended effect (GMP) or not exceeding 4% when added alone or 0.6% when added with vinyl acetate.

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