DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97D–0148]

International Conference on Harmonisation; Draft Guideline on Impurities: Residual Solvents; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft guideline entitled ''Impurities: Residual Solvents.'' The draft guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft guideline recommends acceptable amounts of residual solvents in pharmaceuticals for the safety of the patient, and recommends the use of less toxic solvents in the manufacture of drug substances and dosage forms.

DATES: Written comments by June 16, 1997.

ADDRESSES: Submit written comments on the draft guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Copies of the draft guideline are available from the Drug Information Branch (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–4573.

FOR FURTHER INFORMATION CONTACT:

Regarding the guideline: John J. Gibbs, Center for Drug Evaluation and Research (HFD–820), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–3490.

Regarding the ICH: Janet J. Showalter, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–0864.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

At a meeting held on November 7, 1996, the ICH Steering Committee agreed that a draft guideline entitled ''Impurities: Residual Solvents'' should be made available for public comment. The draft guideline is the product of the Quality Expert Working Group of the ICH. Comments about this draft will be considered by FDA and the Quality Expert Working Group.

Residual solvents in pharmaceuticals are organic volatile chemicals that are used or produced in the synthesis of drug substances or excipients, or in the preparation of drug products. They are not completely removed by practical manufacturing techniques. The draft guideline recommends acceptable amounts of residual solvents in pharmaceuticals for the safety of the patient. The draft guideline recommends the use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents. The draft guideline applies to residual solvents in drug substances, excipients, and drug products, and to all dosage forms and routes of administration. The draft guideline does not apply to potential new drug substances, excipients, or drug products used during the clinical research stages of development, nor does it apply to existing marketed drug products.

Appendices 4, 5, and 6 (toxicity data for Class 1, Class 2, and Class 3 solvents) are not published with the draft guideline, but may be seen at the Dockets Management Branch (address above) and are available via the Internet using the World Wide Web (WWW) (http://www.fda.gov/cder/guidance.htm).

This guideline represents the agency's current thinking on acceptable amounts of residual solvents in pharmaceuticals. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Interested persons may, on or before June 16, 1997, submit to the Dockets Management Branch (address above) written comments on the draft guideline. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. An electronic version of this guideline is available via Internet using the WWW '(http://www.fda.gov/cder/guidance.htm).

The text of the draft guideline follows:

Impurities: Residual Solvents

1. Introduction

The objective of this guideline is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The guideline recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.

Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced in the synthesis of drug substances or excipients, or in the preparation of drug products. They are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical parameter in the synthetic process. This guideline does not address solvents deliberately used as excipients nor does it address solvates.

Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality based

requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data. Some solvents that are known to cause unacceptable toxicities (Class 1, Table 1) should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. Some solvents associated with less severe toxicity (Class 2, Table 2) should be limited in order to protect patients from potential adverse effects. Ideally, less toxic solvents (Class 3, Table 3) should be used where practical. The complete list of solvents included in this guideline is given in Appendix 1.

The lists are not exhaustive and other solvents can be used and later added to the list. Recommended limits of Class 1 and 2 solvents or classification of solvents may change as new safety data become available. (The process for updating and maintaining the guideline is under review by the ICH Steering Committee.) Supporting safety data in a marketing application for a new drug product containing a new solvent may be based on concepts in this guideline or the concept of qualification of impurities as expressed in the guideline for drug substances (Q3A, Impurities in New Drug Substances) or drug product (Q3B, Impurities in New Drug Products) or all three guidelines.

2. Scope of the Guideline

Residual solvents in drug substances, excipients, or drug products are within the scope of this guideline. Therefore, testing should be performed for residual solvents when production or purification processes are known to result in the presence of such solvents. Although manufacturers may choose to test the drug product, a cumulative method may be used to calculate the residual solvent levels in the drug product from the levels in the ingredients used to produce the drug product. If the calculation results in a level below that recommended in this guideline, no testing of the drug product for residual solvents need be considered. If, however, the calculated level is above the recommended level, the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent level to within the acceptable amount. The drug product should also be tested if a Class 1 or Class 2 solvent is used during its manufacture. If no Class 1 or Class 2 solvent is used in the manufacture or purification of the drug substance, excipient, or drug product, then a statement by the applicant or vendors to that effect would be acceptable and no testing would be necessary.

This guideline does not apply to potential new drug substances, excipients, or drug products used during the clinical research stages of development, nor does it apply to existing marketed drug products.

The guideline applies to all dosage forms and routes of administration. Higher levels of residual solvents may be acceptable for short-term (e.g., 30 days or less) or local application. Justification for these levels should be made on a case-by-case basis.

Given the implications of this guideline for the pharmaceutical industry and suppliers, a period of transition (approximately 2 years) will be provided when the guideline is finalized and implemented according to regional procedures (Step 5). See Appendix 2 for additional background information related to residual solvents.

3. General Principles

3.1 Classification of Residual Solvents by Risk Assessment

The term ''tolerable daily intake'' (TDI) is used by the International Program on Chemical Safety (IPCS) to describe exposure limits of toxic chemicals, and the term ''acceptable daily intake'' (ADI) is used by the World Health Organization (WHO) and other national and international health authorities and institutes. The new term ''permitted daily exposure'' (PDE) is defined in the present guideline as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing values for ADI's of the same substance.

Residual solvents assessed in this guideline are listed in Appendix 1 by common names. They were evaluated for their possible risk to human health and placed into one of three classes as follows:

(1) Class 1 solvents: Solvents to be avoided—

Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.

(2) Class 2 solvents: Solvents to be limited—

Nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity; solvents suspected of other significant but reversible toxicities.

(3) Class 3 solvents: Solvents with low toxic potential—

Solvents with low toxic potential to man; no health based exposure limit is needed. Class 3 solvents have PDE's of 50 milligrams (mg) or more per day.

3.2 Methods for Establishing Exposure Limits

See Appendix 3 for an explanation of the method used to establish exposure limits.

3.3 Options for Describing Limits of Class 2 Solvents

Two options are available when setting limits for Class 2 solvents.

Option 1: The concentration limits in parts per million (ppm) stated in Table 2 can be used. They were calculated using equation (1) below by assuming a product mass of 10 grams (g) administered daily.

$$(1) \quad \text{Concentration (ppm)} = \frac{1000 \times \text{PDE}}{\text{dose}}$$

Here, the PDE is given in terms of mg/day and dose is given in g/day.

These limits are considered acceptable for all substances, excipients, or products whatever the dose and use. Therefore, this option may be applied if the daily dose is not known or fixed. Any excipient or drug substance that meets the limits given in Option 1 therefore may be used in any drug product. However, it is not considered necessary for each component of the drug product to comply with the limits given in Option 1.

Option 2: The PDE in terms of mg/day as stated in Table 2 can be used with the known maximum daily dose and equation (1) above to determine the concentration of residual solvent allowed in drug product. Such limits are considered acceptable provided that it has been demonstrated that the level has been reduced to the practical minimum, i.e., the limits are realistic in relation to the manufacturing capability and reflect contemporary manufacturing standards.

Option 2 may be applied by adding the amounts of a residual solvent present in each of the components of the drug product. The sum of the amounts of solvent per day should be less than that given by the PDE.

Consider an example of the use of Option 1 and Option 2 applied to acetonitrile in a drug product. The permitted daily exposure to acetonitrile is 4.1 mg per day; thus the Option 1 limit is 410 ppm. The maximum administered daily mass of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and content of residual acetonitrile is given in the following table.

Component	Amount in formulation	Acetonitrile content	Daily exposure
Drug substance	0.3 g	800 ppm	0.24 mg
Excipient 1	0.9 g	400 ppm	0.36 mg
Excipient 2	3.8 g	800 ppm	3.04 mg

Component	Amount in formulation	Acetonitrile content	Daily exposure
Drug product	5.0 g	728 ppm	3.64 mg

Excipient 1 meets the Option 1 limit, but the drug substance, excipient 2, and drug product do not meet the Option 1 limit. Nevertheless, the product meets the Option 2 limit of 4.1 mg per day and thus conforms to the recommendations in this guideline.

Consider another example using acetonitrile as residual solvent. The maximum administered daily mass of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and content of residual acetonitrile is given in the following table.

Component	Amount in formulation	Acetonitrile content	Daily exposure
Drug substance	0.3 g	800 ppm	0.24 mg
Excipient 1	0.9 g	2,000 ppm	1.80 mg
Excipient 2	3.8 g	800 ppm	3.04 mg
Drug product	5.0 g	1,016 ppm	5.08 mg

In this example, the product meets neither the Option 1 nor the Option 2 limit according to this summation. The manufacturer could test the drug product to determine if the formulation process reduced the level of acetonitrile. If the level of acetonitrile was not reduced during formulation to the allowed limit, then the manufacturer of the drug product should take steps to reduce the amount of acetontirile in the drug product. If all of these steps fail to reduce the level of residual solvent, in exceptional cases the manufacturer could provide a summary of efforts made to reduce the solvent level to meet the guideline value, and provide a risk-benefit analysis to support allowing the product with residual solvent at a higher level.

3.4 Analytical Procedures

Residual solvents are typically determined using chromatographic techniques such as gas chromatography. Any harmonized procedures for determining levels of residual solvents as described in the pharmacopoeias should be used, if feasible. Otherwise, manufacturers would be free to select the most appropriate validated analytical procedure for a particular application. If only Class 3 solvents are present, a nonspecific method such as loss on drying may be used.

Validation of methods for residual solvents should conform to ICH guidelines ''Validation of Analytical Procedures: Definition and Terminology'' and ''Validation of Analytical Procedures: Methodology.''

4. Limits of Residual Solvents

4.1 Solvents to Be Avoided

Solvents in Class 1 should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect. However, if their use is unavoidable in order to produce a drug product with a significant therapeutic advance, then their levels should be restricted as shown in Table 1, unless otherwise justified. Toxicity data for Class 1 solvents are summarized in Appendix 4. The solvent 1,1,1,-Trichloroethane is included in Table 1 because it is an environmental hazard. The stated limit of 1500 ppm is based on a review of the safety data.

TABLE 1.—CLASS 1 SOLVENTS IN PHARMACEUTICAL PRODUCTS (SOLVENTS THAT SHOULD BE AVOIDED)

Solvent	Concentration Limit ppm	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1,500	Environmental hazard

4.2 Solvents to Be Limited

Solvents in Table 2 should be limited in pharmaceutical products. PDE's are given to the nearest 0.1 mg/day and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of determination. Precision should be determined as part of the validation of the method. Available toxicity data are summarized in Appendix 5.

TABLE 2.—CLASS 2 SOLVENTS IN PHARMACEUTICAL PRODUCTS

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3,880
1,2-Dichloroethene	18.7	1,870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1,090

TABLE 2.—CLASS 2 SOLVENTS IN PHARMACEUTICAL PRODUCTS—Continued

Solvent	PDE (mg/day)	Concentration Limit (ppm)
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethyleneglycol	3.1	310
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3,000
2-Methoxyethanol	0.5	50
Methylbutyl ketone	0.5	50
Methylcyclohexane	11.8	1,180
N-Methylpyrrolidone	48.4	4,840
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene[1]	21.7	2,170

[1] usually 60% m-xylene, 14% p-xylene, 9% o-xylene with 17% ethyl benzene.

4.3 Solvents with Low Toxic Potential

Solvents in Class 3 (shown in Table 3) may be regarded as less toxic and of lower risk to human health. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies. It is considered that amounts of these residual solvents of 50 mg per day or less (corresponding to 5000 ppm or 0.5 percent under Option 1) would be acceptable without justification. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice. Available toxicity data for Class 3 solvents are summarized in Appendix 6.

TABLE 3.—CLASS 3 SOLVENTS WHICH SHOULD BE LIMITED BY GMP OR OTHER QUALITY-BASED REQUIREMENTS

Acetic Acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl Acetate	Methylethyl ketone
tert-Butylmethyl ether	Methylisobutyl ketone
Cumene	2-Methyl-1-propanol
Dimethylsulfoxide	Pentane
Ethanol	1-Propanol
Ethyl acetate	1-Pentanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	Tetrahydrofuran

4.4 Additional Solvents

The following solvents (Table 4) may also be of interest to manufacturers of excipients, drug substances, or drug products. However, no adequate toxicological data on which to base a PDE were found. Manufacturers should supply justification for residual levels of these solvents in pharmaceutical products.

TABLE 4.—SOLVENTS FOR WHICH NO ADEQUATE TOXICOLOGICAL DATA WERE FOUND

1,1-Diethoxypropane	Methylisopropyl ketone
1,1-Dimethoxymethane	Methyltetrahydrofuran
2,2-Dimethoxypropane	Petroleum ether
Isooctane	Trichloroacetic acid
Isopropyl ether	Trifluoroacetic acid

Glossary

Genotoxic carcinogens: Carcinogens that produce cancer by affecting genes or chromosomes.

LOAEL: Abbreviation for lowest-observed-adverse effect level.

LOEL: Abbreviation for lowest-observed effect level.

Lowest-observed-adverse effect level: The lowest dose of a substance in a study or group of studies that produces biologically significant increases in frequency or severity

of harmful effects in the exposed humans or animals.

Lowest-observed effect level: The lowest dose of substance in a study or group of studies that produces biologically significant increases in frequency or severity of any effects in the exposed humans or animals.

Modifying factor: A factor determined by professional judgment of a toxicologist and applied to bioassay data to relate that data safely to humans.

NEL: Abbreviation for no effect level.

Neurotoxicity: The ability of a substance to cause adverse effects on the nervous system.

NOAEL: Abbreviation for no-observed-adverse effect level.

No effect level: The dose of substance at which there are no biologically significant increases in frequency or severity of any effects in the exposed humans or animals.

NOEL: Abbreviation for no-observed effect level.

No-observed-adverse effect level: The dose of substance at which there are no biologically significant increases in frequency or severity of harmful effects in the exposed humans or animals.

No-observed-effect level: The dose of substance at which there are no biologically significant increases in frequency or severity of any observed effects in the exposed humans or animals.

PDE: Abbreviation for permitted daily exposure.

Permitted daily exposure: The maximum acceptable intake per day of residual solvent in pharmaceutical products.

Reversible toxicity: The occurrence of harmful effects that are caused by a substance and which disappear after exposure to the substance ends.

Strongly suspected human carcinogen: A substance for which there is no epidemiological evidence of carcinogenesis but there are positive genotoxicity data and clear evidence of carcinogenesis in rodents.

Teratogenicity: The occurrence of structural malformations in a developing fetus when a substance is administered during pregnancy.

Appendix 1. List of Solvents Included in the Guideline

(Note: The chemical structures have been deleted.)

Solvent	*Other Names*	*Class*
Acetic acid	Ethanoic acid	Class 3
Acetone	2-Propanone Propan-2-one	Class 3
Acetonitrile		Class 2
Anisole	Methoxybenzene	Class 3
Benzene	Benzol	Class 1
1-Butanol	*n*-Butyl alcohol Butan-l-ol	Class 3
2-Butanol	*sec*-Butyl alcohol Butan-2-ol	Class 3
Butyl acetate	Acetic acid butyl ester	Class 3
tert-Butylmethyl ether	2-Methoxy-2-methyl-propane	Class 3
Carbon tetrachloride	Tetrachloromethane	Class 1
Chlorobenzene		Class 2
Chloroform	Trichloromethane	Class 2
Cumene	Isopropylbenzene (1-Methyl)ethylbenzene	Class 3
Cyclohexane	Hexamethylene	Class 2
1,2-Dichloroethane	*sym*-Dichloroethane Ethylene dichloride Ethylene chloride	Class 1
1,1-Dichloroethene	1,1-Dichloroethylene Vinylidene chloride	Class 1
1,2-Dichloroethene	1,2-Dichloroethylene Acetylene dichloride	Class 2
Dichloromethane	Methylene chloride	Class 2
1,2-Dimethoxyethaneether	Ethyleneglycol dimethyl Monoglyme Dimethyl Cellosolve	Class 2
N,N-Dimethylacetamide	DMA	Class 2
N,N-Dimethylformamide	DMF	Class 2
Dimethyl sulfoxide	Methylsulfinylmethane Methyl sulfoxide DMSO	Class 3
1,4-Dioxane	p-Dioxane [1,4]Dioxane	Class 2
Ethanol	Ethyl alcohol	Class 3
2-Ethoxyethanol	Cellosolve	Class 2
Ethyl acetate	Acetic acid ethyl ester	Class 3
Ethyleneglycol	1,2-Dihydroxyethane 1,2-Ethanediol	Class 2
Ethyl ether	Diethyl ether Ethoxyethane 1,1′-Oxybisethane	Class 3
Ethyl formate	Formic acid ethyl ester	Class 3
Formamide	Methanamide	Class 2
Formic acid		Class 3
Heptane	n-Heptane	Class 3
Hexane	n-Hexane	Class 2
Isobutyl acetate	Acetic acid isobutyl ester	Class 3
Isopropyl acetate	Acetic acid isopropyl ester	Class 3
Methanol	Methyl alcohol	Class 2

Solvent	Other Names	Class
2-Methoxyethanol	Methyl Cellosolve	Class 2
Methyl acetate	Acetic acid methyl ester	Class 3
3-Methyl-l-butanol	Isoamyl alcohol Isopentyl alcohol 3-Methylbutan-l-ol	Class 3
Methylbutyl ketone	2-Hexanone Hexan-2-one	Class 2
Methylcyclohexane	Cyclohexylmethane	Class 2
Methylethyl ketone	2-Butanone MEK Butan-2-one	Class 3
Methylisobutyl ketone	4-Methylpentan-2-one 4-Methyl-2-pentanone MIBK	Class 3
2-Methyl-l-propanol	Isobutyl alcohol 2-Methylpropan-l-ol	Class 3
N-Methylpyrrolidone	1-Methylpyrrolidin-2-one 1-Methyl-2-pyrrolidinone	Class 2
Nitromethane		Class 2
Pentane	*n*-Pentane	Class 3
1-Pentanol	Amyl alcohol Pentan-l-ol Pentyl alcohol	Class 3
1-Propanol	Propan-1-ol Propyl alcohol	Class 3
2-Propanol	Propan-2-ol Isopropyl alcohol	Class 3
Propyl acetate	Acetic acid propyl ester	Class 3
Pyridine		Class 2
Sulfolane	Tetrahydrothiophene 1,1-dioxide	Class 2
Tetrahydrofuran	Tetramethylene oxide Oxacyclopentane	Class 3
Tetralin	1,2,3,4-Tetrahydro-naphthalene	Class 2
Toluene	Methylbenzene	Class 2
1,1,1-Trichloroethane	Methylchloroform	Class 1
1,1,2-Trichloroethene	Trichloroethene	Class 2
Xylene[1]	Dimethybenzene Xylol	Class 2

[1] Usually 60% m-xylene, 14% p-xylene, 9% o-xylene with 17% ethyl benzene

Appendix 2. Additional Background

A2.1 Environmental Regulation of Organic Volatile Solvents

Several of the residual solvents frequently used in the production of pharmaceuticals are listed as toxic chemicals in the Environmental Health Criteria (EHC) monographs and the Integrated Risk Information System (IRIS). The objectives of such groups as the International Programme on Chemical Safety (IPCS), the U.S. Environmental Protection Agency (EPA), and the U.S. FDA include the determination of acceptable exposure levels. The goal is protection of human health and maintenance of environmental integrity against the possible deleterious effects of chemicals resulting from long-term environmental exposure. The methods involved in the estimation of maximum safe exposure limits are usually based on long-term studies. When long-term study data are unavailable, shorter term study data can be used with modification of the approach such as use of larger safety factors. The approach described therein relates primarily to long-term or *lifetime exposure of the general population* in the ambient environment, i.e., ambient air, food, drinking water, and other media.

A2.2 Residual Solvents in Pharmaceuticals

Exposure limits in this guideline are established by referring to methodologies and toxicity data described in EHC and IRIS monographs. However, some specific assumptions about residual solvents to be used in the synthesis and formulation of pharmaceutical products should be taken into account in establishing exposure limits. They are as follows:

(1) Patients (not the general population) use pharmaceuticals to treat their diseases or for prophylaxis to prevent infection or disease.

(2) The assumption of lifetime patient exposure is not necessary for most pharmaceutical products but may be appropriate as a working hypothesis to reduce risk to human health.

(3) Residual solvents are unavoidable components in pharmaceutical production and will often be a part of drug products.

(4) Residual solvents should not exceed recommended levels except in exceptional circumstances.

(5) Data from toxicological studies that are used to determine acceptable levels for residual solvents should have been generated using appropriate protocols such as those described, for example, by the Organization for Economic Cooperation and Development, EPA, and the FDA Red Book.

Appendix 3. Methods for Establishing Exposure Limits

The Gaylor-Kodell model of risk assessment (Gaylor, D. W., and R. L. Kodell, ''Linear Interpolation Algorithm for Low Dose Assessment of Toxic Substance,'' *Journal of Environmental Pathology and Toxicology*, 4:305, 1980) is appropriate for Class 1 carcinogenic solvents. Only in cases where reliable carcinogenicity data are available should extrapolation by the use of mathematical models be applied to setting exposure limits. Exposure limits for Class 1 solvents could be determined with the use of a large safety factor (i.e., 10,000 to 100,000) with respect to the NOEL. Detection and quantitation of these solvents should be by state-of-the-art analytical techniques.

Acceptable exposure levels in this guideline for Class 2 solvents were established by calculation of PDE values according to the procedures for setting exposure limits in pharmaceuticals (*Pharmacopeial Forum*, Nov.-Dec. 1989) and the method adopted by IPCS for Assessing Human Health Risk of Chemicals (Environmental Health Criteria 170, WHO, 1994). These methods are similar to those

used by the U.S. EPA (IRIS) and the U.S. FDA (Red Book) and others. The method is outlined here to give a better understanding of the origin of the PDE values. It is necessary to perform these calculations in order to use the PDE values tabulated in section 4 of this document.

PDE is derived from the NOEL or the LOEL in the most relevant animal study as follows:

$$PDE = \frac{NOEL\ (or\ LOEL) \times Weight\ Adjustment}{Modifying\ Factors}$$

The PDE is preferably derived from a NOEL. If no NOEL is obtained, the LOEL may be used. Modifying factors proposed here, for relating the data to humans, are the same kind of ''uncertainty factors'' used in Environmental Health Criteria (Environmental Health Criteria 170, WHO, Geneva, 1994) and ''modifying factors'' or ''safety factors'' in *Pharmacopeial Forum*. The assumption of 100 percent systemic exposure is used in all calculations regardless of route of administration.

The modifying factors are as follows:

Interspecies differences:

Differences from animals to human.

Max. 12; e.g., factors of 1 for human, 2 for dogs, and 12 for mice.

Intra-individual differences:

Individual difference in humans.

Factor of 10 is generally given for all organic solvents and 10 is used consistently in this guideline.

Quality and type of available data:

Duration of study; lack of determination of NOEL.

Max. 10; e.g., a factor of 1 is used for a study that lasts at least one-half lifetime (1 year for rodents, 7 years for dogs). A factor of 2 used for a 6-month study in rodents, 5 for a 13-week study, and 10 for a study of 4 weeks or less. When LOEL is used, a factor up to 10 could be used depending on the severity of the toxicity.

Additional modifying factors:

In cases where the NOAEL is derived for critical effects such as nongenotoxic carcinogenicity, neurotoxicity, or teratogenicity.

Max. 10; e.g., factor of 10 when teratogenicity is not accompanied by significant maternal toxicity. A factor of 3 or 5 might be used for less severe toxicity.

The weight adjustment compensates for the difference in body weight between the experimental animal and humans. This guideline assumes a body weight of 50 kilograms (kg) for humans. It is recognized that some adult patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine a PDE. Adjustments may be made for pharmaceuticals intended for the pediatric population.

The expressions for PDE in this document are given in the following format:

$$PDE = \frac{NOEL\ (or\ LOEL) \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

where:

F1 = A factor to account for extrapolation between species.

F1 = 5 for extrapolation from rats to humans.

F1 = 12 for extrapolation from mice to humans.

F1 = 2 for extrapolation from dogs to humans.

F1 = 2.5 for extrapolation from rabbit to humans.

F1 = 10 for extrapolation from other animals to humans.

F2 = A factor of 10 to account for variability between individuals.

F3 = A variable factor to account for toxicity studies of short-term exposure.

F4 = A factor that may be applied in cases of severe toxicity. In studies of reproductive toxicity, the following factors are used:

F4 = 1 for fetal toxicity associated with maternal toxicity.

F4 = 5 for fetal toxicity without maternal toxicity.

F4 = 5 for a teratogenic effect with maternal toxicity.

F4 = 10 for a teratogenic effect without maternal toxicity.

F5 = A variable factor that may be applied if the NEL was not established.

As an example of the application of this equation, consider the toxicity study of acetonitrile in mice that is reported in Appendix 5. The NOEL is calculated to be 50.7 mg $kg^{-1}day^{-1}$. The PDE for acetonitrile in this study is calculated as follows:

$$PDE = \frac{50.7\ mg\ kg^{-1}\ day^{-1} \times 50\ kg}{12 \times 10 \times 5 \times 1 \times 1} = 4.22\ mg\ day^{-}$$

In this example,

F1 = 12 to account for the extrapolation from mice to humans.

F2 = 10 to account for differences between individual humans.

F3 = 5 because the duration of the study was only 13 weeks.

F4 = 1 because no severe toxicity was encountered.

F5 = 1 because the NEL was determined.

Calculations in the appendices follow this format.

The following values are used in the calculations in this document:

Rat body weight	425 g
Pregnant rat body weight	330 g
Mouse body weight	28 g
Pregnant mouse body weight	30 g
Guinea pig body weight	500 g
Rhesus monkey body weight	2.5 kg
Rabbit body weight (pregnant or not)	4 kg
Beagle dog body weight	11.5 kg
Rat respiratory volume	290 liter (L)/day
Mouse respiratory volume	43 L/day
Rabbit respiratory volume	1,440 L/day
Guinea pig respiratory volume	430 L/day
Human respiratory volume	28,800 L/day
Dog respiratory volume	9,000 L/day
Monkey respiratory volume	1,150 L/day
Mouse water consumption	5 milliliter (mL)/day
Rat water consumption	30 mL/day
Rat food consumption	30 g/day

The equation for an ideal gas, PV = nRT, is used to convert concentrations of gases used in inhalation studies from units of ppm to units of mg/L or mg/cubic meter (m^3). Consider as an example the inhalation study of carbon tetrachloride (molecular weight 153.84) reported in Appendix 4.

$$\frac{n}{V} = \frac{P}{RT} = \frac{300 \times 10^{-6}\ atm \times 153840\ mg\ mol^{-1}}{0.082\ L\ atm\ K^{-1}\ mol^{-1} \times 298\ K} = \frac{46.15\ mg}{24.45\ L} = 1.89\ mg/L$$

The relationship 1000 L = 1 m^3 is used to convert to mg/m^3.

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