Residual solvents classification: -

Residual solvents: -

Organic solvents that are used in manufacturing process of the drug substances, excipients and drug product are called Residual solvents.

The residual solvents are not completely removed by practical manufacturing techniques.

Moreover, residual solvents affect the yield by reacting with the drug mixture components and somehow toxic to the intake, they must be identified, Quantified and evaluated.

Residual solvents are classified according to their Toxicity levels and Permitted Daily Exposure (PDE) and Risk assessment

Classification of Residual solvents based on Risk assessment: -

Category	**Risk Level**
Class-I	Highly Toxic Strongly suspected Human Carcinogens Environmental Hazard
Class-II	Moderately Toxic Possible causative agents of other irreversible toxicity Example: - Nongenotoxic animal Carcinogens Neurotoxicity (or) Teratogenicity
Class-III	Low Toxic No health-based exposure limit is needed

Procedure for establishing Exposure limits for Residual solvents: -

The following formulae shall be used for the procedure for establishing the Exposure limits for Residual solvents

$$PDE = \frac{NOEL * Weight\ adjustment}{F1*F2*F3*F4*F5}$$

Where,

NOEL = No observed effect level

Weight adjustment is the body weight of the intake

F factor variable values that are safety factors and can be elaborated as follows

F1 is the factor to account for extrapolation between species

F1 variable value	Extrapolation between species
2	Dogs to Humans
3	Monkeys to Humans
5	Rats to Humans
10	Other animals to Humans
12	Mice to Humans

F1 takes into account the comparative surface area to body weight ratios for the species concerned and for man.

Surface area (S) is calculated as

$$S = kM^{0.67}$$

M = body weight

K = 10 (constant)

F2 is the variable factor of account for variability between individuals.

F2 has the constant value for all the living forms. It is calculated as "**10**" universally

F3 is the variable factor for toxicity studies of short-term exposure for rodents and non-rodents.

F3 variable value	Short-term exposure time	
	Rodents	**Non rodents**
1	Half-life (1 year)	Half-life (7 years)
1	Reproductive studies for full organogenesis	
2	6 months	3.5 years
5	3 months	2 years
10	For shorter duration	

In all cases, the higher factor has been used for study durations between the time points (e.g., a factor of 2 for a 9-month rodent study).

F4 is the variable factor that may be applied in cases of severe toxicity like

Nongenotoxic carcinogenicity (The mechanism in which the chemical capable of producing cancer by some secondary mechanism not related to direct gene damage such as *phenobarbital, carbon tetrachloride, or diethylstilbestrol.)*

Neurotoxicity (The mechanism occurs when the exposure to natural or manmade toxic substances (neurotoxicants) alters the normal activity of the nervous system such as *platinum-based agents, taxanes, vinca alkaloids, proteasome inhibitors, and thalidomide analogs.)*

Teratogenicity (The ability of a drug to cause fetal abnormalities or deformities. *Drugs, alcohol, chemicals and toxic substances are examples of teratogens.*)

In studies of reproductive toxicity, the following factors are used: -

F4 variable value	**Toxicity category**
1	fetal toxicity associated with maternal toxicity
5	fetal toxicity associated without maternal toxicity
5	teratogenic effect with maternal toxicity
10	teratogenic effect without maternal toxicity

F5 is the variable factor that may be applied if the no-effect level (NOEL) or the lowest-observed effect level (LOEL) was not established.

The factor of **up to 10** can be used depending on the severity of the toxicity differs by weight, sex, paediatrics.

If the solvent was present in a formulation specifically intended for paediatric use, an adjustment for a lower body weight would be appropriate.

Class-I Residual solvents Category: -

Class-I Residual solvents are highly toxic in nature and must be avoided in the manufacturing process.

However, if the Class-I Residual solvents are necessary for the process, they must be quantified and evaluated.

Class 1 residual solvents could be determined with the use of a large safety factor (i.e., 10,000 to 100,000) with respect to the No observed-effect level (NOEL)

Class-I Residual solvents		
Solvent	**Conc Limit (ppm)**	**Remarks**
Benzene	2	Carcinogen
Carbon Tetrachloride	4	Toxic and Environmental Hazard
1,2- Dichloroethane	5	Toxic and Environmental Hazard
1,1- Dichloroethane	8	Toxic and Environmental Hazard
1,1,1- Trichloroethane	1500	Toxic and Environmental Hazard

Class-II Residual solvents Category: -

Class-II residual solvents were established by calculation of PDE values according to the procedures for setting exposure limits in pharmaceuticals, and the method adopted by IPCS for Assessing Human Health Risk of Chemicals (Environmental Health Criteria 170, WHO, 1994).

Class-II Residual solvents can be determined by two ways

a) Concentration (ppm) of the Residual solvent present in the compound (either Drug substance, Excipient or the Drug product)

b) PDE limit of the Residual solvent in the compound (either Drug substance, Excipient or the Drug product)

   As the Residual solvents used throughout the manufacturing process of the Drug product and will be present in every compound of starting material like Drug substances and Excipients, the Residual solvents shall be within the limits of the specifications provided in the Guidelines.

   Residual solvents in each substance participating in the process shall be either within the limits of Concentration (ppm) or PDE (mg/day) in every stage of manufacturing process of the Drug product.

   The following formulae can be used for calculating the limits of Residual solvents: -

$$\text{Concentration (ppm)} = \frac{1000 * \text{PDE (mg/day)}}{\text{Dose (g/day)}}$$

$$\text{PDE} = \frac{\text{Dose (g/day)} * \text{Concentration (ppm)}}{1000}$$

If all drug substances and excipients in a formulation meet the limits for the concentration (ppm), these components may be used in any proportion.

These limits are considered acceptable for all drug substances, excipients, and drug products. Therefore, this option may be applied if the daily dose is not known or fixed.

If the ppm limits exceeds in the components, the summation of obtained daily exposure (mg) of all the components in the formulation shall below the given PDE of the Residual solvent.

Consider an example for the formulation of a drug product of 5g with Residual solvent content limits of 4.1mg (410ppm): -

Formulation	Taken (g)	Residual solvent content (ppm)	Daily exposure (mg) obtained
API	0.3	800	0.24
Exciepient-1	0.9	400	0.36
Exciepient-2	3.8	800	3.04
Drug product	5.0	728	3.64

In the above example, the Excipient-I is below the given Residual solvent content level i.e., 410ppm and the rest has above the ppm limit.

However, the sum of amounts of Residual solvent in the Daily exposure (mg) obtained is below 4.1mg in the drug product, the formulation meets the specification limits of PDE of the Residual solvent.

Class-II Residual solvents		
Solvent	**Conc Limit (ppm)**	**PDE (mg/day)**
Acetonitrile	410	4.1
Chlorobenzene	360	3.6
Chloroform	60	0.6
Cyclohexane	3880	38.8
1,2- Dichloroethene	1870	18.7
1,2- Dimethoxy ethane	100	1
N, N- Dimethylacetamide	1090	10.9
N, N- Dimethylformamide	880	8.8
1,4- Dioxane	380	3.8
2-Etahoxyethanol	160	1.6
Ethylene glycol	620	6.2
Formamide	290	2.9
Hexane	290	2.9
Methanol	3000	30
2-Methoxyethanol	50	0.5
Methyl butyl ketone	50	0.5
Methylcyclohexane	1180	11.8
Methylene chloride	600	6
N-Methyl pyrrolidone	530	5.3
Nitromethane	50	0.5
Pyridine	200	2
Sulfolane	160	1.6
Tetrahydrofuran	720	7.2
Tetralin	100	1
Toluene	890	8.9
Trichloroethylene	80	0.8
Xylene	2170	21.7

Class-III Residual solvents Category: -

Class-III Residual solvents are less toxic or negligible compared to the Class-I and Class-II Category. However, they shall be limited as specified.

Unless otherwise stated in the individual monograph, Class-III residual solvents are limited to not more than 50 mg per day (corresponding to 5000 ppm or 0.5%)

If a Class 3 solvent limit in an individual monograph is greater than 50 mg per day, that residual solvent should be identified and quantified.

Class-III Residual solvents
Acetic acid
Acetone
Anisole
1- Butanol
2- Butanol
Butyl acetate
tert-Butyl methyl ether
Cumene
Dimethyl sulfoxide
Ethanol
Ethyl acetate
Ethyl ether
Ethyl formate
Formic acid
Heptane
Isobutyl acetate
Isopropyl acetate
Methyl acetate
3-Methyl-1-butanol
Methylethylketone
Methyl isobutyl ketone
2-Methyl-1-propanol
Pentane
1-Pentanol
1-Propanol
2-Propanol
Propyl acetate

Other Residual solvents for which no adequate toxicology data was found and are used in the formulation process are mentioned in the below table.

Others
1,1-Diethoxypropane
1,1-Dimethoxymethane
2,2-Methoxymethane
Isooctane
Isopropyl ether
Methyl isopropyl ketone
Methyl tetrahydrofuran
Hexane
Trichloroacetic acid
Trifluoro acetic acid