ABSTRACT

Impurities in drug substances and drug products have been important regulatory issues in the Office of Generic Drugs by having significant impact on the approvability of Abbreviated New Drug Application (ANDAs). Organic solvents are commonly used in the pharmaceutical industry as reaction media, in separation and purification of synthesis products and also for cleaning of equipments. As residual solvents are not desirable substances in a final product, different methods for their removal may be used, provided they fulfill safety criteria. After the drying process, analysis need to be performed to check if amounts of solvents used at any step of the production do not exceed acceptable limits (taken from ICH Guideline or from pharmacopoeias). Also new solvents like supercritical fluids or ionic liquids are developed to replace traditional organic solvents in the pharmaceutical production processes. This review was grafted to provide information regarding OVI and/or residual solvent.

Key words: organic solvents, residual solvents, acceptable limits.

INTRODUCTION

Organic solvents are constantly present in the pharmaceutical production processes. The organic solvents are widely used in pharmaceutical industry[1]. Residual solvents in pharmaceuticals, commonly known as organic volatile impurities (OVIs), are chemicals that are either used or produced during the manufacture of active pharmaceutical ingredients (APIs), excipients and drug products[2]. They are usually used at any step of the synthesis pathway of an active substance or excipients, and sometimes during the drug product formulation process. These solvents cannot be completely removed from the final yield by practical manufacturing practices such as freeze drying and drying at high temperature under vacuum. Therefore, some residual solvents may remain in drug substance material. While solvents play a key role in the production of pharmaceuticals, many of the solvents used have toxic or environmentally hazardous properties. Presence of this unwanted impurities may influence the efficacy & safety the pharmaceutical products[3]. But sometimes the presence of some impurities may not deleteriously impact on drug quality if therapeutic efficacy that similar to or greater than the drug substance itself. Nevertheless, a drug substance can considered as compromised with respect to purity even if contains an impurity with superior pharmacological or toxicological properties. Solvents known to cause unacceptable toxicity should be avoided unless their use can be justified on the basis of a risk-benefit assessment. So identification & isolation of impurities are more important. It is identified & isolated by using various analytical methods such as Mass spectrometry, Fourier Transform ion Cyclotron Resonance Mass Spectroscopy (FTCRRMS), Nuclear Magnetic Resonance (NMR), High Performance Liquid Chromatography (HPLC) etc[4]. By keeping in view the importance of impurities in pharmaceutical products, different pharmacopoeias such as British Pharmacopoeia (BP) and United State Pharmacopoeia (USP) has incorporated limits to allowable levels of impurities present in the APIs or formulation. The International Conference on Harmonization (ICH) has also published guidelines on impurities in new drug substance. Residual solvents should not exceed recommended levels, except in exceptional circumstances. Data from toxicological studies that are used to determine acceptable levels for residual solvents should be generated using appropriate protocols, such as those described for example, by Organization for Economic Co-operation and Development (OECD) and the US Food and Drug Administration (FDA) Red Book.

In this article, many aspects of organic solvents used in drug product development and manufacturing are presented (sources and types, acceptable limits and regulations, solvents removal) and new ideas of their replacement with the technologies used in other industries will be mentioned.

SOURCES OF IMPURITIES[5-7]:

Starting materials
These are the materials that are used to begin the synthesis of an APIs. There is a limit test for p-amino phenol, which may be present in starting materials or may be intermediate for others.

Intermediates
The compounds, produced during synthesis of the desired materials are called intermediates. Impurities found in various sources of precursors (sassafras oil, safrol, isosafrol, piperonal), intermediates (beta-nitroisosafrol, piperonylmethylketone (PMK)) and final product (3,4-methylenedioxyamphetamine (MDMA)).

Penultimate intermediate (Final intermediates)
As the name suggests, this is the last compound in the synthesis chain prior to the production of the desired compound. 3,5-Dihydroxyphenylglycine is a crucial amino acid monomer in the nonribosomalglycopeptide antibiotic vancomycin. This nonproteinogenic amino acid is constructed from malonyl-CoA by a set of four enzymes, DpgC-D, in the biosynthetic cluster. DpgC is an unusual metal-free, cofactor-free enzyme that consumes oxygen during the conversion of 3,5-dihydroxyphenylacetyl-CoA (DPA-CoA) to the penultimate intermediate 3,5-dihydroxyphenylglyoxyxate (DGPx). We show that in anaerobic incubations, DpgC catalyzes the exchange of the C2-methylenehydrogens of DPA-CoA at unequal rates, consistent with enzyme-mediated formation of the substrate-derived C2-carbanion as an early intermediate. Incubations with (18)O reveal that DpgC transfers both atoms of an oxygen molecule to DGPx product.

By-products
The unplanned compound produced in the reaction are generally called By-products. In paracetamol bulk, diacetylated paracetamol may form as a By-product.
Interaction products
This is a slightly more comprehensive term than the two described above (by-products and transformation products). However, it is more difficult to evaluate in that it considers interactions that could occur between various chemicals - intentionally or unintentionally. Two types of interaction products that can be commonly encountered are drug substance - excipient interactions and drug substance - container/closer interactions.

Related products
This term tends to suggest that the impurity is similar to the drug substance. Hydrates in Isoniazide which produce hepatotoxicity.

Degradation products
These are the compound produced because of decomposition of material of interest or APIs. The degradation of penicillins and cephalosporins. The presence of β-lactam ring as well as that of an amino group in the C6/C7 chain play critical role in the degradation.

TYPES OF IMPURITY
1. According to ICH guidelines [8] impurities associated with APIs are classified in to following categories:-
   (a) Organic impurities
      E.g. starting materials, Process related impurities, Intermediates, Degradation products
   (b) Inorganic impurities
      E.g. Salts, Catalysts, Ligands, Heavy metals
   (c) Residual solvents
      Organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products.
   (d) Other materials
      E.g. Filter aids, Charcoal

2. According to United State Pharmacopoeias (USP), impurities are categorized as follows[9, 10]:
   (1) Impurities in official articles
      a. Foreign substances: The materials that are introduced by contamination or adulteration, not as a consequence of synthesis or preparation, are labeled foreign substances. E.g. pesticides in oral analgesics.
      b. Toxic impurities: These impurities have significant undesirable biological activity.
      c. Concomitant components: Bulk pharmaceuticals chemicals may contain concomitant components. E.g. Antibiotics that are mixtures and are geometric and optical isomer.
      d. Signal impurities: These impurities include some process related impurities or degradation products that provide key information about the process.

(2) Ordinary impurities
The species of impurities in bulk pharmaceutical chemicals that are innocuous by virtue of having no significant undesirable biological activity in the amounts present are called ordinary impurities.

(3) Organic volatile impurities
OVI's are generally solvents used in the synthesis or during the formulation of the drug product. E.g. chloroform, dichloromethane, etc.

DIFFERENCE B/W OVI SOLVENTS AND RESIDUAL SOLVENTS [11]:
Organic Volatile Impurities are called OVI. Its limit is very low. For example, benzene, chloroform, 1, 4-dioxane, ethylene oxide, methylene chloride and trichloroethylene. On the other hand, Residual Solvents (RS), have higher limits as compared to OVI. Residual solvents refer to the amount that is not removed during the purification of the drug product. The OVI solvents are now included in Residual solvents. Suppose these solvents we are using earlier in preformulation, not using in process but we determine the solvents because these solvents are toxic. Its PDE is very low. There are many different solvents which are used in pharmaceutical manufacturing. Previously this test was called Organic Volatile Impurities (OVI). As most of you probably already know, major changes to USP <467> are on the horizon (July 1, 2007). These changes have been in the works for a few years now, in an effort to harmonize USP requirements to the European Pharmacopoeia (EP). The first change is in the title of the Chapter itself: Residual Solvents (RS) is replacing Organic Volatile Impurities (OVI). The new RS chapter now potentially tests for 53 individual solvents, instead of the four under OVI. However, the test methodology has been simplified, as the Chapter now describes only headspace conditions for analysis, similar to the old OVI Method IV.

ICH HARMONISED TRIPARTITE GUIDELINE [IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS Q3C (R3)] [8]
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 or remains after the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents 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. However, the content of solvents in such products should be evaluated and justified. 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.

SCOPE OF THE GUIDELINE
Residual solvents in drug substances, excipients, and in drug products are within the scope of this guideline. Therefore, testing should be performed for residual solvents when production or purification processes. It is only necessary to test for solvents that are used or produced in the manufacture or purification of drug substances, excipients or drug product. 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 equal to or 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. Drug product should also be tested if a solvent is used during its manufacture. This guideline does not apply to potential new drug substances, excipients or drug products used during the clinical research stage 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 in certain cases such as short term (30 days or less) or topical application. Justification for these levels should be made on a case by case basis.
GENERAL PRINCIPLES
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 "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 and structures. They were evaluated for their possible risk to human health and placed into one of three classes as follows:

Class 1 solvents: Solvents to be avoided
Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.
E.g. Benzene, Carben tetrachloride, 1,1-Dichlorobenzene, etc

Class 2 solvents: Solvents to be limited
Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.
E.g. Acetoniitrile, Chlorobenzene, Chloroform, Cyclohexane, 1, 4-Dioxane, etc.

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 PDEs of 50 mg or more per day. E.g. Acetone, Anisol, 1-Butanol, Cumene, Ethyl ether, etc.

Class 4 solvents: Solvents for which no toxicological data have been found
Solvents for which no adequate toxicological have been found. E.g. 1,1-Dioxy-propane, Trifluorooactic acid, Ethyl acetate, etc.

Methods for Establishing Exposure Limits:
The Gaylör-Kodell method of risk assessment, is appropriate for Class 1 carcinogenic solvents. Only in cases where reliable carcinogenicity data are available should extrapolation be 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 no-observed-effect level (NOEL). Detection and quantitation of these solvents should be state-of-the-art analytical techniques. Acceptable exposure levels in this guideline for Class 2 solvents were established by calculation of PDE values. PDE is derived from the no-observed-effect level (NOEL), or the lowest-observed-effect level (LOEL) in the most relevant animal study as follows:

\[ PDE = \frac{NOEL \times \text{Weight Adjustment}}{F_1 \times F_2 \times F_3 \times F_4 \times F_5} \]

The PDE is derived preferably from a NOEL. If no NOEL is obtained, the LOEL may be used.

The modifying factors are as follows:
\( F_1 = A \text{ factor to account for extrapolation between species} \)
\( F_2 = A \text{ factor to account for extrapolation from rats to humans} \)
\( F_3 = A \text{ factor to account for extrapolation from mice to humans} \)
\( F_4 = A \text{ factor to account for extrapolation from rabbits to humans} \)
\( F_5 = A \text{ factor to account for extrapolation from monkeys to humans} \)
\( F_6 = A \text{ factor to account for extrapolation from other animals to humans} \)
\( F_7 = A \text{ factor to account for extrapotation to from the comparative surface area; body weight ratios for the species concerned and for man} \)

Surface area (S) is calculated as:
\[ S = kM^{0.66} \]

In which, \( M \) = body mass, and the constant \( k \) has been taken to be 10.

\( F_2 = A \text{ factor of 10 to account for variability between individuals} \)

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

\( F_3 = A \text{ variable factor to account for toxicity studies of short-term exposure} \)

\( F_3 = 1 \) for studies that last at least one half lifetime (1 year for rodents or rabbits; 7 years for cats, dogs and monkeys).
\( F_3 = 1 \) for reproductive studies in which the whole period of organogenesis is covered.
\( F_3 = 2 \) for a 6-month study in rodents, or a 3.5-year study in non-rodents.
\( F_3 = 5 \) for a 3-month study in rodents, or a 2-year study in non-rodents.
\( F_3 = 10 \) for studies of a 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.

\( F_4 = A \text{ factor that may be applied in cases of severe toxicity, e.g. non-genotoxic carcinogenicity, neurotoxicity or teratogenicity} \)

In studies of reproductive toxicity, the following factors are used:
\( F_4 = 1 \) for fetal toxicity associated with maternal toxicity
\( F_4 = 5 \) for fetal toxicity without maternal toxicity
\( F_4 = 5 \) for a teratogenic effect with maternal toxicity
\( F_4 = 10 \) for a teratogenic effect without maternal toxicity
\( F_5 = A \text{ variable factor that may be applied if the no-effect level was not established} \)

When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity. The weight adjustment assumes an arbitrary adult human body weight for either sex of 50 kg. This relatively low weight provides an additional safety factor against the standard weights of 60 kg or 70 kg that are often used in this type of calculation. 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. If the solvent was present in a formulation specifically intended for pediatric use, an adjustment for a lower body weight would be appropriate.

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 ppm stated in Table 2 can be used. They were calculated using equation given below by assuming a product mass of 10 g administered daily.

\[ \text{Con. (ppm)} = \frac{1000 \times \text{PDE}}{\text{Dose}} \]

Here, 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. Therefore this option may be applied if the daily dose is not known or fixed. If all excipients and drug substances in a formulation meet the limits given in Option 1, then these components may be used in any proportion. No further calculation is necessary provided the daily dose does not exceed 10 g. Products that are administered in doses greater than 10 g per day should be considered under Option 2.

Option 2: It is not necessary for each component of the drug product to comply with the limits given in Option 1. 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 the calculated maximum content of residual acetonitrile are given in the following table.
Analytical Procedures

Residual solvents are typically determined using chromatographic techniques such as gas chromatography. Other methods are LC-MS, HPLC, Mass Spectroscopy. Any harmonised 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 non-specific method such as loss on drying may be used. Solvents are used frequently to dissolve film-coating material to facilitate application onto compressed tablets. These tablets are subjected to air drying to remove all organic solvents from the coat of finished product. The residual levels of these organic solvents in tablet core and film coats are critical, because they cause undesirable side effects.

LIMITS OF RESIDUAL SOLVENTS

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. 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>
<thead>
<tr>
<th>Solvent</th>
<th>Concentration Limit (ppm)</th>
<th>Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>2</td>
<td>Carcinogen</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>4</td>
<td>Toxic and environmental hazard</td>
</tr>
<tr>
<td>1,2-Dichloroethane</td>
<td>5</td>
<td>Toxic</td>
</tr>
<tr>
<td>1,1-Dichloroethene</td>
<td>8</td>
<td>Toxic</td>
</tr>
<tr>
<td>1,1,1-Trichloroethane</td>
<td>1500</td>
<td>Environmental hazard</td>
</tr>
</tbody>
</table>

Solvents to Be Limited

Solvents in given table should be limited in pharmaceutical products because of their inherent toxicity. PDEs 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.

Table 2: Class 2 solvents in pharmaceutical products.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>PDE (mg/day)</th>
<th>Concentration limit (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetonitrile</td>
<td>4.1</td>
<td>410</td>
</tr>
<tr>
<td>Chlorobenzene</td>
<td>3.6</td>
<td>360</td>
</tr>
<tr>
<td>Chloroform</td>
<td>0.6</td>
<td>60</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>38.8</td>
<td>3880</td>
</tr>
<tr>
<td>1,2-Dichloroethane</td>
<td>18.7</td>
<td>1870</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>6.0</td>
<td>600</td>
</tr>
<tr>
<td>N.N.</td>
<td>10.9</td>
<td>1090</td>
</tr>
<tr>
<td>Dimethylacetamide</td>
<td>8.8</td>
<td>880</td>
</tr>
<tr>
<td>N.N.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimethylformamide</td>
<td>1.4-Dioxane</td>
<td>3.8 380</td>
</tr>
<tr>
<td>2-Ethoxyethanol</td>
<td>1.6</td>
<td>160</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>6.2</td>
<td>620</td>
</tr>
<tr>
<td>Formamide</td>
<td>2.2</td>
<td>220</td>
</tr>
<tr>
<td>Hexane</td>
<td>2.9</td>
<td>290</td>
</tr>
<tr>
<td>Methanol</td>
<td>30.0</td>
<td>3000</td>
</tr>
<tr>
<td>2-Methoxyethanol</td>
<td>0.5</td>
<td>50</td>
</tr>
</tbody>
</table>

Solvents with Low Toxic Potential

Solvents in Class 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 is no long-term toxicity or carcinogenicity studies for many of the solvents in Class 3. E.g. Isobutyl acetate, Anisole, Isopropyl acetate, Ethanol, 1-Pentanol, Ethyl acetate etc.

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% 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.

Solvents for which No Adequate Toxicological Data was Found

The following solvents may also be of interest to manufacturers of excipients, substances, or drug products. However, no adequate toxicological data on which to base a PDE was found. Manufacturers should supply justification for residual levels of these solvents in pharmaceutical products. E.g. 1,1-Diethoxypropane, Methylisopropyl ketone, 1,1-Dimethoxyxemethane, Methyltetrahydrofuran , 2,2-Dimethoxypropane, Petroleum ether etc.

WAYS OF AVOIDING ORGANIC SOLVENTS

A large number of efforts have been put to decrease the amount of organic solvents involved in synthesis of API and manufacturing of drug product. Pharmaceutical companies constantly attempt to eliminate the usage of organic solvents by following other industries, those that are more environmentally friendly. The manufacturers try to exchange more toxic solvents to more friendly ones with similar properties (like replacing benzene with toluene) or look for some new innovations. Substances such as water, supercritical fluids, surfaces or interiors of clays, zeolites, alumina, fluorous phases, silica gels and ionic liquids are taken into consideration as a potential reaction media[12].

JAPANESE PHARMACOPOEIA (JP)[13]:

The JP (14th) has adopted the ICH guideline. As per it; residual solvents as those residual organic solvents in pharmaceuticals that should be tested using gas chromatography to comply with the limits specified in the ICH Harmonized Tripartite Guideline.

EUROPEAN PHARMACOPOEIA (EP)[14]:

EP has fully adopted the ICH guideline regarding residual solvents in 1997. In 2000, they started requiring that all currently marketed drug products, as well as those in development or clinical trial, should meet the ICH guidelines. Section 2.4.24 of the 4th edition of EP describes identification and quantification of Class 1 and Class 2 residual solvents. The test methods can be used to identify the majority of Class 1 and Class 2 solvents when they are unknown and as limit tests for Class 1 and Class 2 solvents. The methods can also be used to quantify Class 2 solvents when the limits are 1000 ppm (0.1%) or to quantify Class 3 solvents when required. In 2005, (EP 6th edition) it has been agreed that acceptance criteria for Class II solvents would not be mentioned in the European Pharmacopoeia monographs and that Class I solvents would be included only where it was known that their use was unavoidable in the manufacturing process for the drug substance using the acceptance criteria laid down in the ICH guidelines. Finally, it is also recognized that some specific substances produce solvated forms for which there are frequently higher levels of solvents, for example, Class III solvents co-crystallizing with the active substances for which higher limits than the normal general 0.5% limit may have to be applied. These higher-level Class III solvents would then be named individually on a case-by-case basis where their presence at such levels is considered to be unavoidable. It should be stressed that there is no safety issue relating to such levels since they are low toxicity solvents and the 0.5% threshold is merely a nominal limit.
CONCLUSION

Residual solvents from the processes in the manufacturing of pharmaceuticals are hazardous and cause serious problems and must be removed. Certain methods like thermogravimetric analysis, loss on drying are simple but lack specificity to identify the volatile analyte, spectroscopic and spectrometric methods lacked sensitivity. Whenever organic solvents are used in the production of pharmaceutical products, especially in the last processing steps, the content of residual solvent in the final product should be analyzed. The complete removal of residual level of these solvents is impracticable and traces always remain in the final products. In class 1, the most toxic solvents are included which, unless strongly justified, should be avoided. For the toxic solvents of class 2, the limits are expressed as concentrations (ppm) and additionally in the case of known daily drug intake, by the very important ‘permitted daily exposure’ (PDE). The class 3 includes the solvents with low toxic potential for which the general limit is set at 0.5%. The class 4 includes solvents for which no adequate toxicological data was found.

REFERENCES