Introduction

Xenobiotics referred to as persistent toxic substances (PTS) include a wide range of intentionally produced chemicals as pesticides (DDT, lindane), industrial products (hexachlorobenzene (HCB), polychlorinated biphenyls (PCB), polybrominated diphenylethers (PBDE), phthalates, organotins), as well as unintentional by-products of main thermal origin (polychlorinated dibenzodioxins (PCDD) and furans (PCDF). The introduction of these chemicals into the environment, and the resulting effects, are major issues that raise concern at a national, regional and global scale. PTS are characterised by structural and chemical-physical properties that make them resistant to degradation, lead to bioaccumulation and to long-range transport, this last property determining detectable contaminations in remote areas of the globe. Most PTS are characterised by a wide range of toxic activities. The potential low-dose and long-term effects of PTS include cancer promotion, various neurological and immunological effects and the ability to interfere with the endocrine system, this last characteristic resulting in their inclusion in the list of the endocrine disrupting chemicals (EDC) prioritary for immediate regulatory actions at a Comunitary level. Exposure to PTS mostly occurs through diet, which may account for over 90% of the total exposure.

Following the recommendations of the Intergovernmental Forum on Chemical Safety, the United Nations Environment Programme (UNEP) Governing Council decided in February 1997 that an international action had to be taken to reduce and/or eliminate the emissions of and other PTS present in food, humans and the environment.

Levels of persistent toxic substances in the general population in Italy

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Summary. - Human exposure to persistent toxic substances (PTS) occurs daily, mainly through diet. As a consequence of continuous exposure, and because of their biological persistence, PTS are virtually present in all individuals, stored in their fatty tissues. The exposure of the Italian general population to PTS is a fact of relevance from a public health perspective, because of the number of toxic effects associated to these compounds, possibly occurring even at the current background level of exposure. Despite this, data on PTS concentrations in humans, considered the best dose metric to carry out an adequate risk assessment, are scarce, as shown by the overview of available information we hereafter present. The Convention of Stockholm on persistent organic pollutants (POP), a group of highly toxic PTS, has entered into force last May. This will oblige parties to develop national implementation plans, thus creating a new opportunity to develop more efficient policies to control POP and other PTS present in food, humans and the environment.

Key words: persistent toxic substances, persistent organic pollutants, levels, humans, Stockholm Convention.


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persistent organic pollutants or “POP” (aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, HCB, mirex, toxaphene, PCB, PCDD, PCDF) identified by the international scientific community as the cause of serious environmental and health threats. Accordingly, an International Negotiating Committee (INC) was established with a mandate to prepare an international legal binding instrument for implementing international actions on these POP. These series of negotiations have resulted in the adoption of the Stockholm Convention in 2001, which has become legally binding this year, on the 17th May, by committing governments to eliminate production and environmental releases of these chemicals. In late 90s, with funding from the Global Environment Facility, UNEP implemented a project to regionally assess PTS, with the aim to identify the major sources of PTS in the environment, to reduce or eliminate releases of PTS at a national, regional or global level, and to identify data gaps. The activities undertaken in the project comprised an evaluation of PTS levels in the environment and consequent impact on biota and humans. For the implementation of the project, the globe was divided into twelve regions, one of which is the Mediterranean. The information collected were discussed and reviewed in a series of Regional Technical Workshop, one of which, the “Second Regional Workshop on assessment of (eco)toxicological impact on PTS and transboundary transport” was held in Rome and hosted by ISS in April 2003. The exercise of collecting and interpreting the existing data on the selected PTS resulted into a Regional Report [1] which emphasised the scarcity of data available on PTS levels in humans in Italy and in the Mediterranean Region in general.

Information hereafter presented have been collected within the framework of the above programme; recent data recently obtained from research programmes are also shown.

**PTS levels in the Italian population**

Food being the main exposure route to PTS (>90% for PCDD, PCDF, PCB and HCB), data on PTS daily intakes represent a good basis for risk assessment; total diet studies are in particular considered a very good tool to estimate PTS exposure through food. However, it must be taken into account that PTS body burden (“internal dose”) is the most appropriate dose metric for PTS exposure and the most accurate procedure to correlate PTS dose and the related adverse effects. This particularly holds for classes of congeners with different structure and toxicity as PCB: congener-specific metabolic rates lead infact to different bioaccumulation rates, this determining congener-specific profiles in human tissues different from what observed in environmental and dietary matrices.

In spite of the “weight of evidence” of PTS toxicity for humans, available data on their levels in human tissues show a substantial paucity which appears even more striking if compared to the amount of data available for environmental matrices, and to the increasing amount of data available for food. This scarcity of data on PTS internal dose severely hinders an adequate human risk assessment. Moreover, available data usefulness is biased by a number of factors: most data lack intact representativeness, since the generally small size of population sampled does not allow an extrapolation to the general population. Also, data comparability is in most cases affected by a number of factors inherent to both study design (individual vs/pooled samples, characteristics of the sampled groups as age, sex, kind of the exposure) and to intrinsic factors (type of human specimen, analytical procedure, expression of results, number of congeners/isomers analysed, time of the study). For some PTS, as phthalates, organotins, alkylphenols, and PBDE, the current information on levels in humans appears to be too scarce to make an evaluation of health risks feasible. No data are at present available on levels of aldrin, endrin, chlordane, heptachlor, HCH and mirex in the Italian population. For the other PTS, the data available, although scarce, may represent a basis of information for human risk assessment at the actual levels of contamination, and for possible future evaluation of the toxicological risk deriving from the exposure to the complex mixtures of these compounds present in the human body.

As to sample typology, breast milk, blood, and adipose tissue result to be the human tissues better characterized.

**Human milk**

Human milk has been the object of a number of studies in the last two decades, because of the sanitary concern associated to the exposure of breast-fed infants to PTS, and hence to the need of characterizing the associated risk. Italy has participated to the monitoring programmes periodically carried out by WHO on a number of countries, aimed to assess the levels of PCDD, PCDF and PCB in human milk. These programmes are a very valuable source of high quality data, since the selection of mothers is based on strict criteria and this allows the highest degree of comparability among different countries and years. Mother's age, number of breast-fed infants and dietary habits are in fact crucial parameters for comparability: in particular, the number of breast-fed infants has been shown to progressively decrease the body burden of the most toxic PTS. In the case of the most persistent PTS (PCB, PCDD and PCDF), maternal body burden is reduced up to 50% in the case of three breast-fed children, while mother's age may be responsible for 20-30% increase among different age classes [2, 3].
Table 1 shows the results of the most recent studies on PCDD, PCDF and PCB levels in human milk from Italian women [4, 5]. Results are expressed in dioxin toxicity equivalents (TEQ or TE units) by the use of the WHO-TEF system [8]. Levels of different groups of PCB are shown in the Table. Indeed, because of the presence in biological matrices of PCB congeners with different, structure-dependent, toxicological activities, risk evaluation for humans is correlated to both the determination of the so-called “dioxin-like” congeners (eighteen congeners among which the “coplanars” PCB 77, 81, 126 and 169) usually found in human tissues at levels comparable to dioxins, and to the determination of the “other”, most abundant congeners, present in human tissues in concentrations three orders of magnitude or more higher than the dioxin-like ones. An estimate of the overall contamination from PCB may be obtained by analyzing a number (usually six: PCB 28, 52, 101, 138, 153, 180, seven when dioxin-like PCB 118 is also considered) of “marker” congeners, which represent the most abundant congeners in biological matrices and whose levels have been shown to be constantly correlated to the total amount of PCB.

When a comparison is carried out on dioxin-like compound (PCDD, PCDF and coplanar PCB) and marker PCB levels among the countries enrolled in the “Third round of WHO coordinated exposure study on levels of PCB, PCDD, and PCDF in breast milk” [4], Italian values result to be comparable to those assessed in a number of other European countries (Germany, Spain, The Netherlands, Luxembourg, Belgium) [4].

As far as pesticides are concerned, no recent data are available for Italy.

**Blood and adipose tissue**

Very little information is available on PTS levels in blood. Selected PTS levels determined in a study carried out on Italian nulliparous women of reproductive age are shown in Table 1 [6, 7].

With respect to PCDD and PCDF, although a straightforward comparison between data shown in Table 1 might be biased by a number of factors (age distribution, diet, sex), it is worth noticing that the Italian value (8.9 pg WHO-TE/g lb) appears to be at the lowest bound of the range of PCDD+PCDF body burden figures reported for several European countries, as shown in Table 2 [3, 6, 9-11].

Mean DDT and HCB concentrations in fat sampled in 1997-2000 from 18 subjects living in Central Italy were respectively of 1976 and 335 ng/g wet wt [13]. Such levels were found to be positively correlated to age ($r_s = 0.6; p<0.05$).

PBDE levels of 1.9 pg/g fat (as the sum of the three most abundant congeners PBDE 47, 99 and 153) have

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Year of sampling</th>
<th>Number of subjects</th>
<th>Unit</th>
<th>Level</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Milk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCDD/Fs</td>
<td>2000</td>
<td>40</td>
<td>pgWHO-TE/g, lipid base</td>
<td>13</td>
<td>[4]</td>
</tr>
<tr>
<td>PCDD/Fs</td>
<td>2001</td>
<td>24</td>
<td>pgWHO-TE/g, lipid base</td>
<td>13</td>
<td>[5]</td>
</tr>
<tr>
<td>Dioxin-like PCBs</td>
<td>2000</td>
<td>40</td>
<td>pgWHO-TE/g, lipid base</td>
<td>16</td>
<td>[4]</td>
</tr>
<tr>
<td>Coplanar PCBs</td>
<td>2001</td>
<td>24</td>
<td>pgWHO-TE/g, lipid base</td>
<td>7.6</td>
<td>[5]</td>
</tr>
<tr>
<td>Marker PCBs</td>
<td>2000</td>
<td>40</td>
<td>ng/g, lipid base</td>
<td>250</td>
<td>[4]</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCDD/Fs</td>
<td>2001</td>
<td>10</td>
<td>pgWHO-TE/g, lipid base</td>
<td>8.9</td>
<td>[6]</td>
</tr>
<tr>
<td>Dioxin-like PCBs</td>
<td>2001</td>
<td>10</td>
<td>pgWHO-TE/g, lipid base</td>
<td>8.7</td>
<td>&quot;</td>
</tr>
<tr>
<td>Marker PCBs</td>
<td>2001</td>
<td>10</td>
<td>ng/g, lipid base</td>
<td>120</td>
<td>&quot;</td>
</tr>
<tr>
<td>$p,p'-$DDT</td>
<td>2001</td>
<td>10</td>
<td>ng/g, lipid base</td>
<td>14</td>
<td>De Felip et al., unpublished results</td>
</tr>
<tr>
<td>$p,p'$-DDE</td>
<td>2001</td>
<td>10</td>
<td>ng/g, lipid base</td>
<td>450</td>
<td>&quot;</td>
</tr>
<tr>
<td>HCB</td>
<td>2001</td>
<td>10</td>
<td>ng/g, lipid base</td>
<td>45</td>
<td>&quot;</td>
</tr>
<tr>
<td>PBDEs$^b$</td>
<td>2001</td>
<td>10</td>
<td>ng/g, lipid base</td>
<td>1.9</td>
<td>[7]</td>
</tr>
</tbody>
</table>

(a): grouped into pools; (b): sum of the three most abundant congeners. 47+99+153. PCDD/F: polychlorodibenzodioxins; PCB: polychlorobiphenyls; $p,p'$-DDT: 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane; $p,p'$-DDE: 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene; HCB: hexachlorobenzene; PBDE: polybromodiphenylethers.
been found in blood from Italian women. This value appears lower than levels reported, for the same congeners, for other European Countries as Sweden [14], Germany [15], Belgium [16], Spain [17], which are all around 4 pg/g fat.

Other tissues

PCB, \( p,p' \)-DDE and HCB levels were assessed in samples of follicular fluid from healthy women from Rome enrolled in a study carried out in 2000. PCB concentration was about 900 pg/g fat as the sum of the three main congeners PCB 138, 153, 180 [18]. Congener profile of the 12 most abundant congeners appears to be in good agreement with those reported for other biological matrices (e.g., human blood, mother’s milk). \( p,p' \)-DDE and HCB levels, respectively in the range of 639-830 and 69-73 ng/g fat, fall in the range of lipid-base concentrations normally found in breast milk [19].

Data gaps

In Italy, as in most European countries, the scarcity of data on PTS body burdens is quite severe, also as a result of the lack of a systematic monitoring programme: it is worthwhile to emphasize that a representative study of a general healthy population living in a wide geographic area has never been conducted. As many other countries Italy lacks population indicators on the impact that environmental contamination has on human health. Temporal trends are impossible to assess, essentially because of the limited number of studies, the limited number of subjects analysed and inappropriate reporting of methods by most studies. On the side of toxicology, effects of many PTS are still unknown or not fully clarified, and mechanistic information lacking. This consideration is not limited to classes of compounds of relatively recent interest from a scientific and regulatory standpoint (e.g. PBDE), but it also applies to chemicals which have been under focus for many years. A typical example of this latter case is represented by PCB: the hazard identification for the most abundant congeners is still poorly defined, having the attention of researchers being mainly focused on the “dioxin-like” ones. Moreover, even for those PTS for which a considerable amount of toxicological information is available, low-dose effects, subtle effects and long-term effects are far to have been characterized. An increasing number of studies suggests indeed that some PTS can cause biological effects at levels far below of deemed safe doses. Furthermore, the exposure of the developing organisms, in utero and via breast feeding, may result in subtle effects with respect to highly sensitive endpoints (i.e. neurodevelopmental, endocrine). An additional issue that should be addressed in characterizing the risk associated to PTS is that they are present in human tissues as complex mixtures. This point is very critical, since the characterization of the effects following exposure to complex mixtures of several chemicals still remains one of the most ambitious goals of toxicology. Infact, besides the difficulty to define the mixtures of congeners/ compounds present in human tissues, not necessarily similar to those occurring in the environment, the multiple toxicological interactions occurring in the human body are at present very poorly characterized.

Together with the study of the toxicological properties and mechanisms of actions, obtained in an integrated approach of research, a better knowledge of exposure could help in the protection of the general population. The importance of these issues is clearly stated by the Convention of Stockholm on POP [20], which entered into force on the 17th May 2004. The Convention requires each Party to prepare its National Implementation Plan (NIP) within two years of the date on which the Convention enters into force for it,
describing how it will meet the obligations set. In identifying priorities for initiating future activities to protect human health and the environment from POP, the Convention text clearly states that parties shall encourage and/or undertake appropriate research and monitoring activities aimed to assess presence, levels and trends in humans and the environment, and effects on human health and the environment. In this context the assessment of the degree of contamination of humans by PTS is indicated as necessary to fulfil the governments’ mission to protect the public health, with a special attention to vulnerable groups, in particular infants and children. The ratification of the Stockholm Convention is therefore a welcome opportunity to fill the present data gaps, by launching systematic monitoring programmes on POP and other PTS in the environment, and trends in humans and the environment, and effects on human health and the environment. In this context the assessment of the degree of contamination of humans by PTS is indicated as necessary to fulfil the governments’ mission to protect the public health, with a special attention to vulnerable groups, in particular infants and children. The ratification of the Stockholm Convention is therefore a welcome opportunity to fill the present data gaps, by launching systematic monitoring programmes on POP and other PTS in the environment, and general population.

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