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Modelling ecological and human exposure to POPs in Venice lagoon. Part I — Application of MERLIN-Expo tool for integrated exposure assessment

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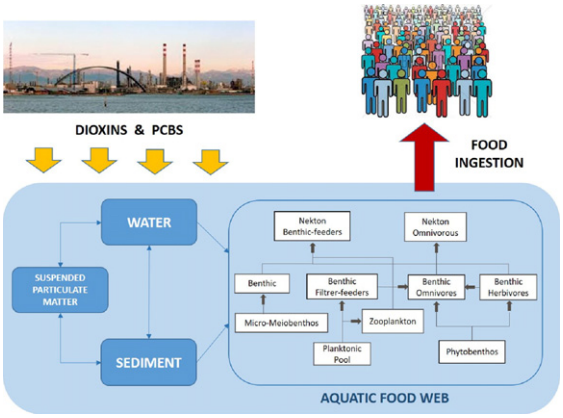
HIGHLIGHTS

- Ecological and human internal exposure to POPs was simulated with MERLIN-Expo
- A long-term exposure scenario was simulated using 5 models from MERLIN-Expo library
- POPs measurements in biota and human serum were used to evaluate model performance
- Simulated internal exposure estimates are in good agreement with biomonitoring data
- The evaluation of internal exposure estimates against benchmarks showed no significant risk

GRAPHICAL ABSTRACT



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ABSTRACT

Industrial and urban emissions over several decades left a legacy of contamination by persistent organic pollutants in the sediments of Venice lagoon (Italy), which might still represent a hazard for the health of ecosystems and population. A new modelling tool for integrated exposure assessment, MERLIN-Expo, was applied to simulate integrated ecological and human exposure to PCBs and dioxins. MERLIN-Expo library provides a set of environmental fate models that can be easily combined to create several scenarios, and coupled to a human intake and a physiologically-based pharmaco-kinetic (PBPK) model to simulate human internal exposure. The Phytoplankton, Invertebrate and Fish models implemented in MERLIN-Expo library were combined to create an aquatic food web and to dynamically simulate bioaccumulation and biomagnification of dioxins and PCBs. Concentrations of PCB and dioxins in water, reconstructed from concentrations in dated sediment cores, were used as time-series inputs to run long term simulations. Estimated concentrations in edible aquatic species were used to estimate daily human intake through the consumption of local seafood. Finally, the application of the PBPK model allowed to explore the accumulation of 2,3,7,8-TCDD and PCB126 in human tissues for several decades. Simulated chemical concentrations in biota were evaluated against monitoring data for four aquatic species, finding an appreciable agreement, with some differences depending on the species and target chemicals. Estimated chemical concentrations in blood were compared to real human biomonitoring data measured in adult

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men. Despite several assumptions included in the assessment framework, simulated concentrations resulted close to measured data (the same order of magnitude or one order of difference). The results allowed performing a preliminary ecological and human health risk assessment for the selected chemicals by evaluating the exposure estimates against benchmark values available in literature. The study provided useful insights for supporting the verification of MERLIN-Expo in a real complex exposure scenario.

1. Introduction

The lagoon of Venice is a superficial basin, located along the northwestern coast of the Adriatic Sea. It can be defined as a transitional environment, characterized by shallow waters (Guerzoni and Tagliapietra, 2006) and influenced by several anthropogenic activities such as industry, fishery, and tourism. These activities have caused in the past and still cause the release in environmental media of a wide range of chemical substances, including persistent organic pollutants (POPs). The most significant sources of POPs can be identified in the industrial area of Porto Marghera (where many chemical industries, oil refining plants, and waste incineration plants were present, today partially dismissed), the treated and untreated municipal wastewater from the city of Venice and surrounding urban centres, contaminant loads from rivers from the catchment area and atmospheric depositions (Collavini et al., 2005; Guerzoni et al., 2005). Lagoon sediments, which keep trace of historical time trends of emissions (Dalla Valle et al., 2005; Frignani et al., 2005), represent the most important secondary source of POPs. Despite the implementation of environmental protection regulations and the application of technologies for emissions control in the last two decades, the affinity of POPs to organic matter and their persistence (Ritter et al., 2007) resulted in a legacy of contaminated sediment in the lagoon of Venice. Due to their resistance to chemical and biological degradation, chemicals like polychlorinated dibenzo-*p*-dioxins and -furans (PCDD/Fs) and polychlorinated biphenyls (PCBs) can indeed be detected in environmental matrices for a long time after their production and release and can represent for many years a hazard to ecosystems and human health (UNEP, 2001). POPs are bioaccumulative and can magnify along aquatic and terrestrial food webs, with high exposure potential for top predators (Kelly et al., 2007). Human populations can be exposed to POPs through different pathways, but food of animal origin often represents the most significant sources of POP exposure for humans (Moser and McLachlan, 2002). Therefore, if a comprehensive and realistic risk assessment is pursued, the link between ecosystems' contamination and human exposure should deserve special attention when investigating POP fate and effects.

Considering the persistence of POPs, their potential for bioaccumulation and biomagnification, and the possibility to cause adverse biological effects even long time after exposure, risk assessment of POPs requires approaches and tools adequate to realistically reconstruct long term exposure scenarios, covering many decades or the entire human life span, and able to incorporate at the same time both ecological and human targets. The potentialities of integrating ecological and human exposure assessment, referred to as "Integrated Exposure Assessment", has been recently highlighted by Ciffroy et al. (2015), who described the benefits of adopting common modelling frameworks, including the development of common exposure scenarios and the harmonization of monitoring and modelling activities covering both the ecological and human health domains.

In recent years several studies focused on modelling bioaccumulation and biomagnification of PCB and dioxins in terrestrial and aquatic ecosystems in different environments by means of food web models, which include several species at different trophic levels. Some examples are provided by Armitage and Gobas (2007), Arnot and Gobas (2004), Figueiredo et al. (2014), Gobas and Arnot (2010), Gobas and Wilcockson (2003), Micheletti et al. (2008) and Nfon et al. (2011).

At the same time, many authors investigated the exposure of human populations to PCB and dioxins through several modelling approaches. Human exposure can be evaluated in terms of "external exposure" (WHO-IPCS, 2005), by combining data on chemical concentrations in contact media (air, soil, water, food) with frequency and duration of contact or food daily intakes and with absorption across the contact surface to estimate the overall daily dose of chemical entering the body. However, in recent years, attention moved towards the estimate of internal exposure, that is the dose to a target tissue or organ, which can be used to characterize more effectively the link between the intake from the environment and the arise of adverse health effects. Pharmacokinetic (PK) models can be developed and applied for this purpose: they describe the fate of chemical compounds in the body by simulating biological processes of absorption, distribution, metabolism and excretion (ADME). More complex models account for organism physiology and can simulate age- and/or gender-dependent changes over time. These models, called physiologically-based pharmacokinetic (PBPK) models, are suitable to predict the determinants of inter- or intra-individual variability on internal dosimetry (Bois et al., 2010).

Several examples of internal exposure modelling for different congeners of PCBs and dioxins are available in literature. Some authors developed and/or applied PK or PBPK models to reconstruct past exposure scenarios or to simulate possible future exposure (Alcock et al., 2000; Bu et al., 2015; Sweetman et al., 2000; Ulaszewska et al., 2012), to explore the linkage between internal exposure and relevant determinants such as age, diet, and reproductive behaviours (Quinn et al., 2010; Quinn and Wania, 2012), to derive POP elimination half-lives (Ritter et al., 2011), or to assess the relationships with variable emissions scenarios or emissions from specific polluting sources (Nadal et al., 2013; Nøst et al., 2015; Schuhmacher et al., 2014).

Only few studies proposed an integrated modelling of ecological and human exposure within a comprehensive assessment. An example is offered by (Czub and McLachlan, 2004), who developed and applied a fugacity-based mechanistic model (ACC-HUMAN) to describe bioaccumulation of lipophilic organic pollutants from air, water and soil to humans, considering aquatic and terrestrial food chain. The model was also coupled to a long-range multimedia fate model by Breivik and colleagues (in the CoZMoMAN model) (Breivik et al., 2010) or to the global transport model Globo-POP (Czub et al., 2008) and further applied in different regional contexts (e.g., Quinn et al., 2010; Quinn and Wania, 2012). However, ACC-HUMAN does not address the kinetic aspects of contaminant distribution in human body (Czub and McLachlan, 2004).

To the best of our knowledge, no previous studies addressed integrated exposure modelling of PCBs and dioxins in the Venice lagoon area. Environmental processes and POP contamination in the Venice lagoon have been the target of different monitoring and research projects and initiatives in the last three decades. Several monitoring campaigns investigated the distribution of PCBs and dioxins in Venice lagoon (e.g., Secco et al., 2005; Venice Water Authority, 1999, 2000a, 2000b) and some studies included the monitoring of chemical concentrations in aquatic species living in the lagoon (e.g., Venice Water Authority, 1999, 2006), but only very few studies investigated the presence of these chemicals in human tissues. Multimedia models and aquatic food web models were applied to explore the fate and transport of POPs in different environmental matrices and bioaccumulation and biomagnification processes along the aquatic food web (Dalla Valle et al., 2003; Micheletti et al., 2008; Sommerfreund et al., 2010). However, a comprehensive modelling of POP behaviour from environmental concentrations to the estimate of human internal concentrations has not been conducted before. Taking into account the toxicity of dioxins

and PCBs, which have been associated to several serious health effects, including cancer, birth defect, neurological impairment, sterility, endocrine disruption (ATSDR, 2000; Ritter et al., 2007; Schecter, 2012), and the scarcity of human biomonitoring studies conducted in the area, the potential utility of predictive modelling tools to explore the relationships between environmental contamination distribution, diet patterns and internal exposure is evident.

MERLIN-Expo tool, recently developed in the frame of 4FUN project (www.4funproject.eu), offers the possibility to perform ecological and human exposure modelling on the same platform, providing a library of models which can be flexibly combined to recreate complex exposure scenarios where both ecological and human targets can be included (Ciffroy et al., this issue). MERLIN-Expo allows to dynamically simulate bioaccumulation in different aquatic species and biomagnification along the aquatic food web and, subsequently, to model human chemical intake and internal exposure (concentrations in different tissues and organs) through a generic PBPK model.

The main objective of this work is to simulate ecological and human exposure to PCBs and dioxins in Venice lagoon, and to test the feasibility of reconstructing long term exposure scenarios by applying the new MERLIN-Expo tool. Moreover, the study aims at evaluating the performance of MERLIN-Expo in integrated exposure modelling through the comparison of model results against real monitoring data, including chemical concentrations in target aquatic species and human biomonitoring data collected in the municipality of Venice.

2. Methods

2.1. Case study

The lagoon of Venice can be divided into three main basins: southern, central and northern lagoon. For the integrated exposure assessment, the central lagoon has been selected as target area: it is close to Porto Marghera industrial area and has been strongly influenced by discharge of contaminants associated to industrial activities. Many studies on superficial sediments showed that the concentrations of persistent organic pollutants such as dioxins and PCBs in the central basin were higher than in other areas (Frignani et al., 2001; Marcomini et al., 1997; Secco et al., 2005; Venice Water Authority, 1999, 2000a,b). At the same time, central lagoon became the most relevant area for local shellfish industry. Biological resources of the lagoon have been exploited since centuries by traditional fishing and farming activities. After the introduction and the extensive diffusion of the bivalve Manila clam (*Tapes philippinarum*, which rapidly replaced the autochthonous species *Tapes decussatus*), since the early 90s the mechanical clam harvesting became the most important activity in the fishing sector, with an annual production of clams up to 40,000 tons. Dredging grounds are mainly concentrated in the central basin of the lagoon, where high nutrient, organic matter, phytoplankton and microphytobenthos concentrations created optimal conditions for clam growth (Pranovi et al., 2003; Sfriso et al., 2005, 2003). Even after the prohibition of fishing activities in the areas close to Porto Marghera (and the identification of suitable areas for clam harvesting), illegal fishing continued in the most contaminated areas (Boscolo et al., 2007). Therefore, adopting a conservative approach, the selection of central lagoon as target areas for exposure modelling allows to consider the worst-case scenario for both ecological and human exposure assessments.

For human exposure assessment, it is worth remembering that the overall body burden of PCBs and dioxins (reflected in blood concentrations) depends on toxico-kinetic processes, governed by age-dependent human physiology and by physico-chemical properties of chemical, as well as on external environmental exposure. Environmental burdens of PCBs and dioxins have changed over the last 70 years, as demonstrated by retrospective studies. For PCBs, a peak of exposure in the 70s has been identified, followed by a decrease since the 80s as consequence of chemical use and emission regulation (e.g., Fensterheim, 1993). It is therefore necessary to reconstruct possible past exposure scenarios to perform lifetime human exposure assessment. Emission data suitable to retrace the historical development of PCB and dioxin contamination in Venice lagoon area are not available. As an alternative, sediment cores proved to be useful in reconstructing temporal contamination trends in Venice area (Frignani et al., 2005; Marcomini et al., 1999), also in combination with modelling approaches (Dalla Valle et al., 2005). In general, a significant increase of organic pollutants in lagoon sediment has been observed since the 1940s, the maximum inputs of contaminants are on average associated with the period '60–70s, then an appreciable decrease was observed. However relative abundance and behaviour of individual substances might follow a different trends depending on emission patterns and chemical characteristics. Concentrations of PCBs and dioxins in different layers of a dated sediment core from central lagoon measured by Frignani et al. (2005) have been selected for the purposes of this study.

With the aim of testing the accuracy of MERLIN-Expo models in predicting ecological and human exposure, measurements of chemical concentrations in biota and human tissues were required. Unfortunately, only few human biomonitoring studies have been performed in the Venice area. The selected study was conducted in 1998, funded by Venice municipality, and it involved 41 volunteers (adult males resident in the municipality of Venice) (Frangipane, 1999; Raccanelli et al., 2007). Concentrations of TCDD/Fs and PCBs were analysed in serum extracted by an isotope dilution method using a relative response factors previously obtained from five standard solutions injections, according to USEPA recommendations (USEPA methods 1613B/94 and 1668A/99). Lipid content of serum was analytically determined for normalization of chemical levels to serum fat content. The volunteers were divided into two groups according to their diet: 22 consumers of large amounts of locally caught fish and shellfish (at least 3 times a week) and 19 persons consuming little quantities of fish of any kind (<2 times a week). For the purpose of the present study, data related to high fish consumers were selected.

For the same time period as human biomonitoring data, measurements of bioaccumulation of PCBs and dioxins were available for four aquatic species, namely *T. philippinarum* (Manila clam), *Carcinus mediterraneus* (green crab), *Zosterisessor ophiocephalus* (goby), and *Chelon labrosus* (seabass) (Venice Water Authority, 1999).

According to the availability and the spatial and temporal comparability of chemical measurements in environmental, biota and human samples, PCB77, PCB126, PCB167, PCB169, PCB170, PCB180, 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD and 1,2,3,4,7,8-HCDD were selected for the ecological exposure assessment, while the full chain assessment (i.e., up to human internal exposure) focused on PCB126 and 2,3,7,8-TCDD.

2.2. Selected MERLIN-Expo models and exposure scenario

MERLIN-Expo is a software tool aimed at performing exposure assessment for both organic and inorganic chemicals for environment, biota and humans. It includes a library of environmental and human exposure models which can be flexibly combined to recreate several exposure scenarios, including different exposure pathways, to explore the evolution of ecological and human exposure (up to internal exposure in target organs/tissues) to chemicals over time (Ciffroy et al., this issue). MERLIN-Expo allows the users to perform both deterministic and probabilistic dynamic simulations of exposure estimates and incorporate a set of functionalities for applying different methods of sensitivity analysis.

Five models (i.e., Phytoplankton, Invertebrate, Fish, Human Intake and Man models) have been selected among those available in MERLIN-Expo library and coupled to recreate the target exposure scenario, as represented in Fig. 1. All models were implemented in the library during 4FUN project, and they are based on previously existing modelling approaches which have been refined and adapted to fit the features and requirements of the new tool and to be compatible one

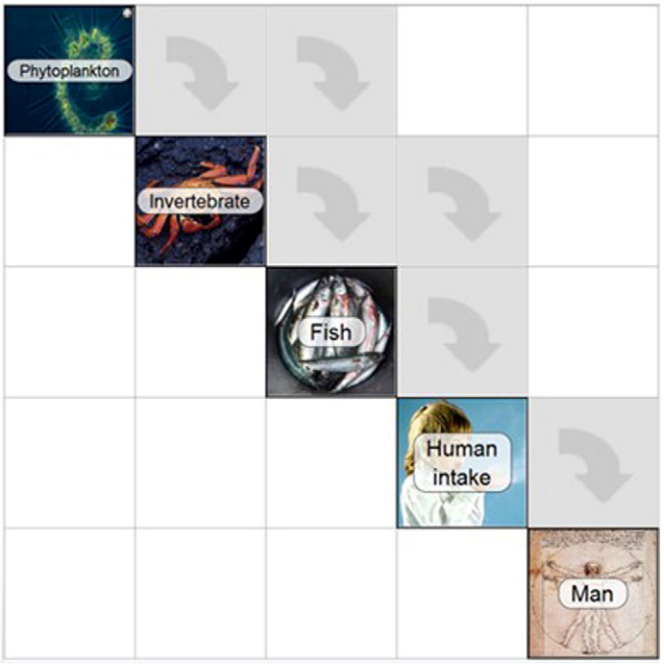

Fig. 1. Models selected for the integrated exposure assessment in Venice lagoon visualized in the MERLIN-Expo matrix interface.

with each other. A short description of the selected model, including appropriate references, can be found in Ciffroy et al. (this issue), and detailed model documentation is available on MERLIN-Expo website (http://merlin-expo.eu/learn/documentation/model-documentation/). Therefore, in the following paragraphs only the goal and the main features of each model are reported.

Phytoplankton, Invertebrate and Fish models allow to dynamically simulate the bioaccumulation of chemicals in aquatic organisms and can be linked to recreate an aquatic food web of various dimensions and complexity. They are based on the "Optimal Modelling for EcotoxicoloGical Applications" (OMEGA) modelling approach proposed by Hendriks and colleagues (Hendriks et al., 2001; Hendriks and Heikens, 2001), with some adaptation needed to fit MERLIN-Expo requirements (e.g., population renewal in time). The Fish and Invertebrate models include two compartments corresponding to two input/output pathways for chemical accumulation, namely the respiratory system and the gastrointestinal tract (GIT) system, while Phytoplankton is represented by a single-compartment model. The main processes simulated by the models are: chemical uptake through respiration, chemical uptake through ingestion of food (preys) or sediment, elimination through respiratory excretion, elimination through egestion, growth and metabolism. For Phytoplankton, uptake from water, elimination and growth are considered.

The Human Intake model allows to estimate chemical daily intakes for human targets through different exposure pathways. This can be considered a kind of "connection model", which has been created ad-hoc to link environmental and human models in MERLIN-Expo. It is composed of a set of equations combining chemical concentrations estimated by other MERLIN-Expo models in environmental matrices (water, soil, dust, atmosphere, etc.) or food items (fish or aquatic invertebrates, grain, leafy vegetables, potato or root) with human daily intake rates (ingestion or inhalation rates) and human activity patterns (time spent indoor/outdoor) to derive the total quantity of chemical(s) ingested or inhaled per day by each individual.

The Man model is a PBPK model composed of 22 compartments representing organs connected through blood flood (Beaudouin et al., 2010) and it is aimed at simulating the evolution of the amounts or concentrations of chemical compounds in tissues and organs of the human body over lifetime. Using as input the amount of inhaled or ingested contaminant, the Man model can predict internal dosimetry of the compound, as concentrations in target tissues that can be linked to toxic effect or in the form of biomarkers of exposure (such as concentration in blood or urine) that can be compared to appropriate reference or guidance threshold values (e.g. biomonitoring equivalents). The model accounts for the following processes: uptake processes (absorption of contaminant by ingestion and inhalation), distribution of the compound in body organs, metabolism by enzymatic processes and excretion from the body. Moreover, it takes into account the evolution of the anatomy and physiology over the lifetime of individuals, simulating all the physiological or biochemical changes arising during the development and growth from birth onwards.

Fig. 1 illustrates the linkages between the selected models, with grey arrows in the matrix representing output(s) of one model used as input(s) to another one. Aquatic food web models (i.e., Phytoplankton, Invertebrate and Fish) are connected based on the prey–predator relationships in the food web: this means that the estimated chemical concentration in each aquatic species and its lipid fraction are used by the subsequent model to estimate chemical dietary intake for the predator organism. Some of the organisms included in the Venice lagoon food web are edible organisms, which are commonly caught or harvested in the lagoon. In order to simulate the consumption of specific fish and shellfish species by local population and estimate human internal exposure to POPs associated with the diet, the aquatic food web models were linked to the Human Intake and to the Man model. For the case at hand, only dietary intake (i.e., ingestion of contaminated fish and seafood) is considered for human exposure. Inhalation is a recognized exposure route for many persistent organic compounds, but its relative contribution to the overall exposure can be considered to be small when compared with dietary exposure (Alcock et al., 2000). Significant dermal contact can usually be restricted to few occupational exposure scenarios. Therefore, these two exposure routes are not further taken into account in human exposure modelling for the Venice lagoon case study.

2.3. Input data

2.3.1. Input data for ecological exposure modelling

In order to simulate the accumulation of target chemicals in aquatic organisms of Venice lagoon, the definition of a site-specific food web structure is required. A food web describes the pattern of trophic relationships among selected species in an ecosystem and provides a simplified representation of biomass and energy flows. Feeding relationships not only expose organisms to contaminants, but also represent a critical process of pollutants transfer, resulting in bio-magnification phenomena as the consequence of dietary uptake (Kelly et al., 2007; Mackay and Fraser, 2000). The characterization of predator-prey interactions is pivotal to understand contamination patterns and associated adverse effects when moving from individuals to the ecosystem level (Rohr et al., 2006).

A site-specific food web for the bioaccumulation assessment in Venice lagoon has been proposed by Micheletti et al. (2008) based on extended literature on Venice lagoon ecosystems assessment and modelling (e.g., Carrer and Opitz, 1999; Libralato et al., 2002; Pranovi et al., 2003). This food web has been slightly adapted for the application of MERLIN-Expo and it includes 17 species plus the sediment compartment, which constitutes part of the diet for some benthic organisms. For some species (Manila clam, *C. labrosus*, *Sparus aurata*, *Dicentrarchus labrax*), adult and juvenile individuals are considered as two separate components in the network, to account for differences in their metabolism, feeding habitat and internal tissue composition.

The proposed food web includes species which have been selected to cover specific trophic roles (primary producers, top predators, etc.) and/or play an important role for fishing activity and can therefore be part of the human diet (i.e., they are also relevant in the perspective of human exposure assessment).

The food web includes two planktonic groups, eight benthonic species/groups, eight nektonic species/groups (19 elements in total plus the sediment compartment). A diagram representing the Venice lagoon food web is presented in Fig. 2 (only main trophic relationships are reported).

Input data required by MERLIN-Expo models are grouped as:

a) "parameters", which are constant over each simulation and can be classified as chemical related parameters (e.g., physico-chemical properties of target chemicals) and biota related parameters (e.g., diet preferences, physiological parameters of selected species);
b) "time series", which are time-dependent environmental data (e.g. concentrations in environmental media such as water or sediment, water temperature).

Phytoplankton, Invertebrate and Fish models require the same chemical-related parameters (i.e., octanol-water partition coefficient, bio-concentration factor, metabolic half-life of chemicals); moreover, Phytoplankton model requires also the water–organic carbon partition coefficient. Contaminants specific parameter values were derived using QSAR models implemented in EPI Suite software (USEPA, 2012a): metabolic half-life of chemicals for organics (Arnot et al., 2008, 2009), bioconcentration factor for organics (Arnot and Gobas, 2003, 2006), water-organic carbon partition coefficient (Schüürmann et al., 2007), and octanol/water partition coefficient (Meylan and Howard, 1995). All input values for the selected substances are reported in Table S1 in SI.

Input values for biological parameters for the species included in the Venice food web have been derived from available literature and free databases and are reported in Table 1 and Table 2.

Fish and Invertebrate models require the user to define the diet preferences of each species included in the simulation. Components of organisms' diet can be either other aquatic organisms, such as invertebrate, fish or phytoplankton species (in this case the parameter to be informed is "Diet preference for food item") or the organic fraction of sediment (in this case the parameter to be informed is "Diet preference for sediments"). In order to better clarify the trophic relationships between the considered species, these data are included all together in the so called "diet matrix", which reports, for each target species, the fraction of each prey/food item over the total dietary intake (in the interval [0; 1]). Diet preferences for the Venice lagoon organisms have been defined according to available literature data and adapting the diet matrix proposed by Micheletti et al. (2008). The diet matrix is reported in Table S2 in SI.

Time dependent input values required by aquatic food web models include water temperature, chemical concentrations in dissolved water, and chemical concentrations in sediment. Water temperature affects organisms' uptake and excretion processes. A constant temperature of 15 °C is assumed for the Venice lagoon. Time series of concentrations of the target chemicals in sediment and in water are required by the food web models to simulate chemical uptake and obtain an estimate of time-dependent chemical concentrations in phytoplankton, invertebrate and fish species. In order to cover the temporal scenario of several decades required by the human exposure assessment, concentration of individual congeners in different layers of a dated sediment core collected in central lagoon (sediment core named "E" in Frignani et al., 2005; Venice Water Authority, 2000b) were used to reconstruct historical trends of sediment contamination. Values between the measured points reported in Table 3 have been interpolated in order to reconstruct continuous temporal trends. Chemical concentrations dissolved in water (reported in Table 3) were calculated starting

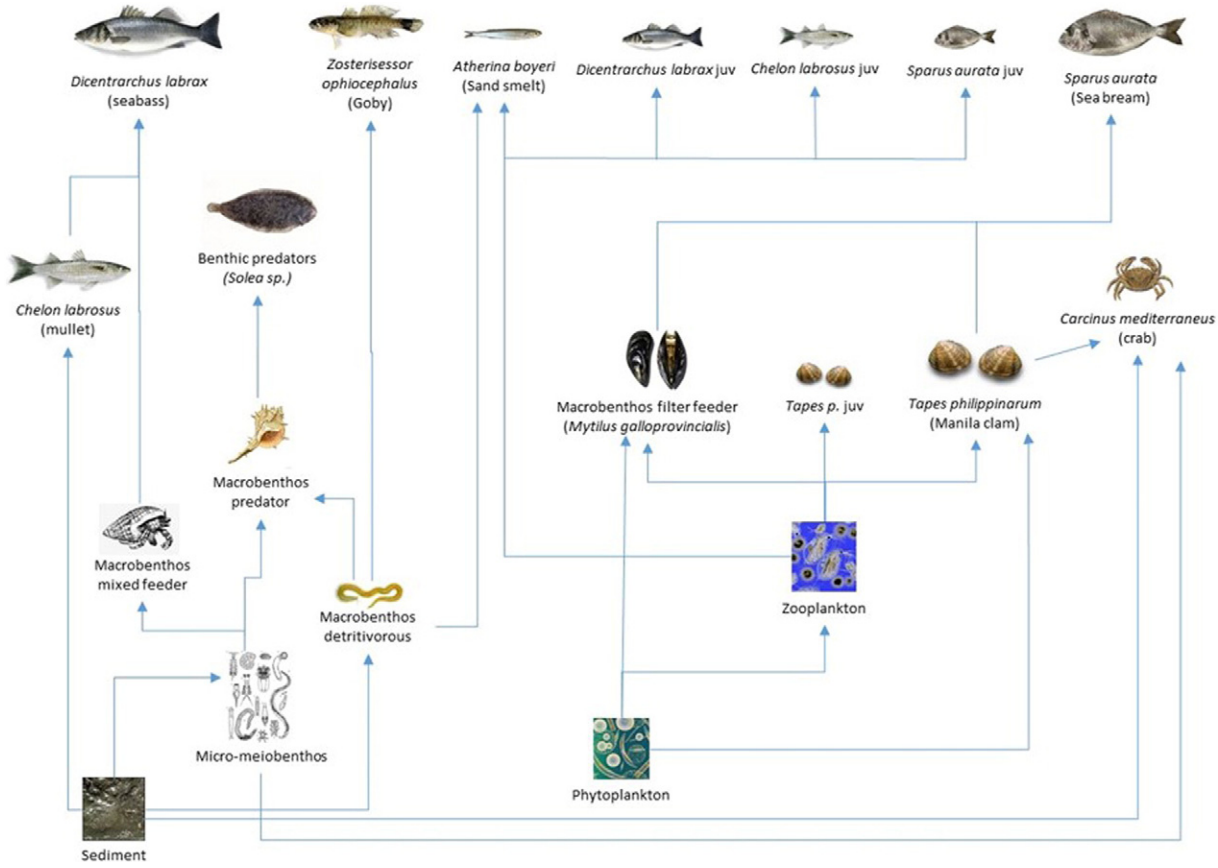

Fig. 2. Aquatic food web for Venice lagoon.
Adapted from Micheletti et al. (2008) *and* Libralato et al. (2002).

Table 1
Input values for biological parameters of Phytoplankton model.

Parameter	Unit	Value	Reference
Allometric rate exponent	Unitless	0.25	Hauck et al. (2011)
Intercept of phytoplankton growth rate	Unitless	0.22	Marañón et al. (2013)
Slope of phytoplankton growth rate	Unitless	0.15	Marañón et al. (2013)
Lipid fraction of phytoplankton	Unitless	0.02	Skoglund et al. (1999), Olenina et al. (2006)
Lipid layer permeation resistance	kg d/kg	97	Hauck et al. (2011)
Lipid layer resistance exponent	Unitless	0.41	Hauck et al. 2011)
Organic carbon fraction of phytoplankton	Unitless	0.29	Skoglund et al. (1999), Olenina et al. (2006)
Phytoplankton cell volume	μm^3	7.68	Olenina et al. (2006)
Water layer diffusion resistance for uptake of chemicals from water	kg d/kg	0.0068	Hauck et al. (2011)

from chemical concentrations in sediment following the approach described in SI.

2.3.2. Input data for human exposure modelling

2.3.2.1. Parameterization of the PBPK model. The Man model in MERLIN-Expo was parameterized for the two target chemicals selected for the human exposure assessment, namely 2,3,7,8-TCDD and PCB126.

Although chemicals absorbed from gut lumen enter the liver first, ingested 2,3,7,8-TCDD and PCB126 were set to enter the blood flow directly in this model, assuming that they pass liver fast enough to avoid accumulation or first pass effects such as metabolic elimination. The option "Ingestion via the liver" available in MERLIN-Expo for this purpose was then used. The absorption rate was obtained by Mclachlan (1993). Only one elimination route was considered in the liver via biliary excretion, since urinary excretion of dioxins and PCBs can be neglected. The excretion rates were set to the values provided by Milbrath et al. (2009) and Ogura (2004). Tissue–blood partition coefficients of liver, kidney, fat, muscle and richly perfused tissue were calculated using dioxin concentration data in human tissues (Iida et al., 1999), or determined based on structural information of the chemicals (Parham et al., 1997). The fat:blood partition coefficients were estimated using a quantitative structure-activity relationship (QSAR) specific to PCBs (Parham et al., 1997). The other tissue:blood partition coefficients were obtained by multiplying the fat:blood partition coefficients by a factor related to the tissue composition. Input values for PBPK model parameters are reported in Table 4.

2.3.2.2. Daily food intakes. The most site-specific information on fish and seafood daily intakes for the municipality of Venice is available in the report "Fish production and fish consumption preferences of families in Venice municipality" (Pedenzini, 1996), based on the results of a survey performed in the different areas of Venice municipality (Venice historical centre; islands and coastal villages; mainland/Mestre city). The estimated average daily intake of fish and seafood in the Municipality was equal to 2168 g/month, equivalent to 72.3 g/day. For individuals living in Venice lagoon islands and coastal villages, the average daily intake increased to 94.7 g/day.

Typology and quantity of food intake vary depending on the age, it is therefore important to consider age dependent food intakes when simulating life time exposure for the same individual. Age dependent intake rates for Italian population were obtained from the INN-CA national survey (Turrini et al., 2001) performed in 1994–96 by the Italian National Food and Nutrition Research Institute (INRAN) based on the investigation of diet habits through individual questionnaires (7-day based survey technique), involving 1978 individuals stratified into four main geographical areas. Data were aggregated into four age groups: children (1 to 9 years), adolescents (10 to 17 years), adults (18 to 63 years) and elderly people (>63 years). Data on daily intake of "fish and seafood (fresh and frozen)" for the different age groups were selected. The ratio between age group average daily intakes and overall average daily intake in INN-CA survey was used to scale Venice daily intake to different age group intakes to get site-specific age dependent intake values.

Ideally, to reconstruct historical exposure, changing diet patterns across different decades should be considered. However, due to the lack of historical data on diet habits in the area in the past (and generally in Italy), mean daily intakes for different age groups have been assumed as constant for all the simulation period.

The survey by Pedenzini (1996) reported also information on diet preferences of local population for specific typologies of fish/seafood, considering the categories "molluscs", "crustaceans" and "fish" and including some indications on most consumed species of fish or shellfish. This information has been used to "subdivide" the age group intake values into several aquatic species contributing to the overall intake, in order to link the outputs of the aquatic food web models (namely, concentrations in aquatic organisms from Fish and Invertebrate models) to the Human Intake model in MERLIN-Expo. The age dependent daily intakes of different types of fish and seafood used as input data to MERLIN-Expo Human Intake model are reported in Table 5 for persons classified as high fish consumers.

2.4. Simulation settings

Using the chain of models described in Section 2.2, MERLIN-Expo was applied to simulate PCBs and dioxins exposure of Venice lagoon aquatic organisms and high fish consumers from local population. Simulations were run for a maximum time period of about 27,000 days (74 years), from 1924 (birth year of the oldest individual) to 1998 (collection of human biomonitoring data). Both deterministic and probabilistic simulations were run: in this paper only deterministic results are presented, while probabilistic parameterization as well as results of probabilistic simulations are included in the companion paper by Radomyski et al. (this issue). Since a long term exposure scenario is considered, where environmental contamination by persistent pollutants and, consequently, food contamination (i.e., exposure of aquatic organisms in the aquatic food web) change over decades, the year of birth influences the overall internal exposure and it is thus necessary to run separate simulations for different individuals born in different years. The tool in fact does not allow to consider individuals born after the starting date of the simulation. Therefore, individual exposure simulations have been run separately with MERLIN-Expo, taking into account the year of birth of study participants (from 1924 to 1972).

2.5. Evaluation of bioaccumulation model performance

The performance of the aquatic food web models was evaluated according to the approach proposed by Arnot and Gobas (2004). Model performance can be expressed quantitatively using model bias (MB_j) calculated for all n chemicals in a single species j:

$$MB_j = 10^{\left(\sum_{i=1}^{n} \frac{\left[\log\left(BAF_{p,i}/BAF_{o,i}\right)\right]}{n}\right)} \quad (1)$$

where BAF_p, BAF_o are predicted and observed bioaccumulation factors, and subscripts i, and j refer to number of chemicals and species respectively.

An overall model performance for all m species (MB) can be calculated as follows:

$$MB = 10^{\left[\sum_{j=1}^{m} \frac{\left(\sum_{i=1}^{n} \frac{\left[\log\left(BAF_{p,i,j}/BAF_{o,i,j}\right)\right]}{n}\right)}{m}\right]}. \quad (2)$$

Table 2
Input values for biological parameters of Invertebrate and Fish models.

Parameter	Allometric exponent	Lipid fraction of invertebrate	Food transport coefficient	Fraction of assimilated food	Lipid layer permeation coefficient	Water layer diffusion resistance for uptake of chemicals from food	Water layer diffusion resistance for uptake of chemicals from water	Age at maturity	Weight at maturity	Fish length at maturity	Intercept of length–weight relationship	Slope of length–weight relationship
Unit	Unitless	Unitless	kg_{fw}/kg_{fw} d	Unitless	kg d/kg	kg d/kg	kg d/kg	d	kg_{fw}	cm	Unitless	Unitless
Invertebrate model												
Zooplankton	0.25	0.05	0.03	0.73	97	0.0002	0.0068	20	3.42E−05			
Micro-meiobenthos	0.25	0.014	0.03	0.73	97	0.0002	0.0068	20	1.00E−04			
Macrobenthos detritivorous	0.25	0.014	0.03	0.73	97	0.0002	0.0068	90	3.20E−04			
Macrobenthos omnivorous filter feeder	0.25	0.012	0.03	0.73	97	0.0002	0.0068	548	6.71E−03			
Tapes philippinarum juv	0.25	0.0125	0.03	0.73	97	0.0002	0.0068	90	1.00E−03			
Tapes philippinarum	0.25	0.0125	0.03	0.73	97	0.0002	0.0068	910	7.00E−03			
Macrobenthos omnivorous mixed feeder	0.25	0.0262	0.03	0.73	97	0.0002	0.0068	90	1.41E−03			
Carcinus mediterraneus	0.25	0.05	0.03	0.73	97	0.0002	0.0068	730	1.02E−02			
Macrobenthos omnivorous predator	0.25	0.05	0.03	0.73	97	0.0002	0.0068	545	1.57E−03			
Fish model												
Atherina boyeri	0.25	0.096	0.03	0.73	97	0.0002	0.0068	1778.5		10.5	0.00603	3.07
Chelon labrosus	0.25	0.068	0.03	0.73	97	0.0002	0.0068	4745		30.3	0.00794	3.12
Chelon labrosus juv	0.25	0.068	0.03	0.73	97	0.0002	0.0068	730		3	0.0091	3.02
Dicentrarcus labrax	0.25	0.1338	0.03	0.73	97	0.0002	0.0068	1095		35.9	0.00891	3.05
Dicentrarcus labrax juv	0.25	0.0076	0.03	0.73	97	0.0002	0.0068	75		3	0.0076	3.2
Nekton carnivorous benthic feeder	0.25	0.08	0.03	0.73	97	0.0002	0.0068	1058.5		32.5	0.0123	2.96
Sparus aurata	0.25	0.0973	0.03	0.73	97	0.0002	0.0068	949		30	0.01259	3.03
Sparus aurata juv	0.25	0.0973	0.03	0.73	97	0.0002	0.0068	365		3	0.00923	3.28
Zosterisessor ophiocephalus	0.25	0.1	0.03	0.73	97	0.0002	0.0068	1659.5		16.3	0.00813	3.07
References	Hauck et al. (2011)	R. Froese et al. (2014), M. Hauck et al. (2011), C. Micheletti et al. (2008), http://www.fishbase.org/	Hauck et al. (2011)	Hauck et al. (2011)	Hauck et al. (2011)	Hauck et al. (2011)	Hauck et al. (2011)	R. Froese et al. (2014) http://www.fishbase.org/	Micheletti et al. (2008), Durbin and Durbin (1978), P. Palmerini et al. (1994), Robinson et al. (2010)	R. Froese et al. (2014) http://www.fishbase.org/	R. Froese et al. (2014) http://www.fishbase.org/	R. Froese et al. (2014) http://www.fishbase.org/

Table 3
Temporal trend of chemical concentrations in sediment and water; reported concentrations in sediment correspond to measured data, while for intermediate years interpolation was applied; concentrations in water were reconstructed according to the approach described in SI.

Year	Sediment depth (cm)	PCB77	PCB126	PCB167	PCB169	PCB180	2,3,7,8-TCDD	1,2,3,7,8-PCDD	1,2,3,4,7,8-HCDD
SEDIMENT (mg/g dw)									
1920	21–18	3.00E−08	5.00E−09	2.00E−08	5.00E−09[a]	1.00E−07	2.50E−10	2.00E−10	4.00E−10
1935	18–15	1.40E−07	2.40E−07	1.20E−07	5.00E−09[a]	6.40E−07	3.00E−10	6.00E−10	1.30E−09
1940	12–15	4.50E−07	1.00E−08	4.00E−07	5.00E−09[a]	9.20E−07	7.00E−10	9.00E−10	1.70E−09
1950	9–12	4.60E−07	1.60E−07	4.40E−07	5.00E−09[a]	1.82E−06	7.00E−10	1.70E−09	4.10E−09
1960	6–9	5.20E−07	4.00E−08	7.00E−07	5.00E−09[a]	1.71E−06	2.50E−10[a]	2.30E−09	3.40E−09
1975	3–6	3.50E−07	4.00E−08	2.61E−06	5.00E−09[a]	5.78E−06	2.50E−10[a]	1.50E−09	2.00E−09
1998	1.5–3	2.30E−07	2.00E−08	7.80E−07	5.00E−09[a]	1.92E−06	4.00E−10	1.30E−09	2.00E−09
WATER (mg/m^3)									
1920	21–18	7.12E−07	2.01E−08	3.88E−09	2.19E−09	5.84E−10	6.11E−10	2.96E−11	3.08E−12
1935	18–15	3.32E−06	9.65E−07	2.33E−08	1.35E−09	3.74E−09	7.33E−10	8.88E−11	1.00E−11
1940	12–15	7.96E−06	2.88E−08	5.39E−08	8.06E−10	3.71E−09	1.21E−09	9.25E−11	9.02E−12
1950	9–12	5.36E−06	2.88E−07	3.59E−08	4.88E−10	4.40E−09	7.52E−10	1.06E−10	1.31E−11
1960	6–9	9.62E−06	1.21E−07	9.96E−08	8.52E−10	7.29E−09	4.57E−10	2.50E−10	1.91E−11
1975	3–6	6.69E−06	1.26E−07	3.86E−07	8.86E−10	2.56E−08	4.74E−10	1.69E−10	1.17E−11
1998	1.5–3	4.62E−06	6.64E−08	1.23E−07	9.42E−10	9.07E−09	8.03E−10	1.56E−10	1.24E−11

[a] Original value below the detection limit (<LOD); a value of LOD/2 has been used.

In general terms, a model tends to over-predict when MB > 1 and tends to under-predict when MB < 1. MB is a geometric mean of the log-normally distributed ratio BAF_p/BAF_o, of all chemicals in all species. Therefore, the 95% confidence interval (CI) of the geometric mean represents the accuracy of the model. MB and its 95% CI include the following sources of error: model parameterisation, model structure, also errors in analytical and empirical data. The analysis of changes in MB values can be used as an indicator of model performance under various scenarios.

2.6. Estimation of Hazard Quotient for ecological and human exposure

From a regulatory or risk assessment perspective, ecological and human exposure estimates provided by MERLIN-Expo can be evaluated against existing quality standards or threshold values with the aim of deriving an estimate of risks posed to the selected ecological or human targets by the considered environmental contaminants, under the assessed scenario(s).

As for ecological risk assessment, traditionally environmental regulation relies on media-based quality guidelines, where chemical concentrations in water or sediment are used to quantify environmental risks considering selected target species or the entire ecosystem. However, water quality criteria for bioaccumulative chemicals should incorporate several specific perspectives in order to be sufficiently protective, such as the consideration of chemical uptake through multiple exposure routes including the diet, long term exposure scenarios and inclusion of all factors affecting chemical bioavailability and bioaccumulation (Sappington et al., 2011). To address all these needs, the tissue residue approach (TRA) has been proposed, based on the use of tissue residue as dose metric when evaluating exposure–response relationships (Meador et al., 2011).

The Oregon Department of Environmental Quality (2007) proposed a Critical Tissue Level (CTL) for fish equal to $6.4 * 10^{-6}$ mg/kg_{fw} for dioxins and PCB in both freshwater and marine environments, expressed as 2,3,7,8-TCDD Toxic Equivalent (TE). CTLs correspond to *concentrations in tissue at or below which approximately 95% of aquatic organisms bearing this residue would be highly unlikely (<5% chance) to experience adverse health effects.*

To obtain an estimate of ecological risk for each fish species, a Hazard Quotient (HQ) for all dioxins and dioxin-like PCBs can be calculated by comparing the exposure concentration (expressed as sum of Toxic Equivalents for the investigated substances) with the toxicity threshold

Table 4
Input values for PBPK model parameters for 2,3,7,8-TCDD and PCB126.

Parameters	2,3,7,8-TCDD	PCB 126
Absorption rate		
Oral	0.97	1
Excretion and metabolism		
Excretion rate in liver ($min^{-1}\cdot kg^{-1}$)	4.257×10^{-7}	–
Clearance in liver ($L\cdot min^{-1}\cdot kg^{-1}$)	–	5×10^{-5}
Partition coefficients		
Adipose	247	152
Adrenal	9.8	20.7
Blood	1	1
Blood_arterial	1	1
Blood_venous	1	1
Bones	9.8	7.6
Bones_NP	1	1
Brain	4.1	18.2
Breast	17	101.8
Gut	9.8	10.5
Gut_lumen	1	1
Heart	9.8	9.3
Kidneys	3.1	7.9
Liver	9.8	7.7
Lungs	4.1	1.6
Marrow	1	109.2
Muscle	17	7.5
Pancreas	9.8	21.8
Sexual_organs	9.8	8.2
Skin	2.5	7.0
Spleen	9.8	2.9
Stomach	9.8	11.3
Stomach_lumen	1	1
Thyroid	9.8	20.7
Urinary_tract	9.8	7.3

Table 5
Age dependent daily intakes of different types of fish and shellfish.

Food items	Daily intake (kg_{fw}/day)			
	Children (1–9)	Adolescents (10–17)	Adults (18–63)	Elderly (>63)
Macrobenthos filter feeders (mussel)	0.005	0.007	0.007	0.006
Tapes philippinarum (Manila clam) and similar sediment dwelling molluscs	0.022	0.032	0.036	0.031
Carcinus mediterraneus (crab)	0.008	0.011	0.012	0.010
Atherina boyeri (sand smelt)	0.003	0.004	0.004	0.004
Chelon labrosus (mullet)	0.006	0.008	0.009	0.008
Dicentrarcus labrax (seabass)	0.008	0.011	0.013	0.011
Sparus aurata (gilt-head bream)	0.008	0.011	0.013	0.011
Zosterisessor ophiocephalus (goby)	0.004	0.006	0.006	0.005

Table 6
Comparison of measured and modelled concentrations of chemicals in selected aquatic species (mg/kg$_{fw}$) for year 1998; ratio m/s represents the ratio of measured and estimated value.

Chemical	Concentration in aquatic species (mg/kg$_{fw}$)											
	Tapes philippinarum			*Carcinus mediterraneus*			*Chelon labrosus*			*Zosterissessor ophiocephalus*		
	Measured[a]	Simulated	Ratio m/s	Measured	Simulated	Ratio m/s	Measured	Simulated	Ratio m/s	Measured[b]	Simulated	Ratio m/s
2,3,7,8-TCDD	1.40E−08[c]	3.90E−07	0.036	1.01E−07	1.66E−07	0.608	6.72E−07	5.27E−08	12.751	8.58E−08	6.42E−09	13.364
1,2,3,7,8-PCDD	2.13E−08[c]	1.96E−06	0.011	1.86E−07	8.33E−07	0.223	7.20E−07	2.80E−07	2.568	1.54E−07	2.03E−08	7.589
1,2,3,4,7,8-HCDD	4.21E−08[c]	5.35E−06	0.008	1.29E−07	2.09E−06	0.062	1.54E−07[c]	7.16E−07	0.215	4.76E−08	2.65E−08	1.795
PCB 77	1.77E−05	3.57E−04	0.050	1.53E−04	2.55E−04	0.600	2.64E−04	1.41E−03	0.187	1.13E−05	4.88E−04	0.023
PCB 126	2.30E−06	5.67E−05	0.041	1.62E−05	5.26E−05	0.308	5.79E−05	3.65E−05	1.586	2.26E−05	6.78E−06	3.333
PCB 167	5.37E−05	2.59E−03	0.021	5.44E−04	2.12E−03	0.257	1.27E−03	1.37E−03	0.925	3.31E−04	1.08E−04	3.068
PCB 169	2.85E−07	1.68E−05	0.017	3.46E−06	1.45E−05	0.238	5.28E−06	1.14E−05	0.463	6.09E−06	8.90E−07	6.846
PCB 170	1.49E−04	8.01E−03	0.019	9.31E−04	5.44E−03	0.171	5.31E−03	4.24E−03	1.251	1.98E−03	1.61E−04	12.277
PCB 180	3.91E−04	1.47E−02	0.027	2.44E−03	9.82E−03	0.248	1.01E−02	7.32E−03	1.380	3.85E−03	2.86E−04	13.453

[a] Mean value estimated from data in three sampling sites.
[b] Mean value estimated from data in four sampling sites.
[c] At least one of the considered measurement values was below the limit of detection (LOD); value equal to half LOD was used in the calculation of the mean.

(i.e., CTL value), as follows:

$$HQ_i = \frac{TEQ_i(PCDDs + DL{-}PCBs)}{CTL} \quad (3)$$

where *i* is the fish species. Toxic Equivalent Factors as defined by WHO for fish species have been used (Van den Berg et al., 1998).

As for human exposure assessment, in order to provide a quantitative evaluation of the obtained exposure estimates, simulated internal concentrations can be compared to a specific Biomonitoring Equivalents (BEs). A BE has been defined as the concentration of a chemical substance in a biological medium (such as blood, urine) that is consistent with existing health-based exposure guidance (Hays et al., 2007). BE have been proposed to be used as screening tool for assisting in the evaluation of general population or specific population biomonitoring data, but are not supposed to serve as diagnostic criteria to evaluate the likelihood of adverse health effects in individual.

Aylward et al. (2008) reviewed available health based exposure guidance value for 2,3,7,8-TCDD and related compound from several agencies and estimated a corresponding BE values for dioxin-like compound measured in blood. They defined a BE of 15 ng TEQ/kg lipid, expressed as lipid-adjusted serum concentration, according to the Minimal Risk Level set by ATSDR for dioxins (based on neurodevelopmental effects in monkey). Serum lipid-adjusted TEQ concentrations of approximately 31 to 74 ng TEQ/kg lipid are consistent with the tolerable daily intakes estimated by the WHO Joint Expert Committee on Food Additives (JECFA), the EC Scientific Committee on Food (ECSCF) and UK Committee on Toxicology (UKCOT) (based on data on reproductive effects in rats). Then, more recently, based on a re-evaluation of Reference Dose (RfD) for 2,3,7,8-TCDD performed by USEPA (2012b), and leading to the definition of a RfD equal to 0.7 pg/kg∗day, a new value of Biomonitoring Equivalent of 21 pg/g serum lipid was defined for adults (older than 20) for dioxin TEQ including dioxins, furans and dioxin-like PCBs (Aylward et al., 2013). This last BE value has been selected for the evaluation of MERLIN-Expo estimates of internal concentration.

For BE based on non-cancer end points (e.g., RfD), a Hazard Quotient can be calculated as follows (Aylward et al., 2013):

$$HQ = \frac{[\text{biomarker}]}{BE}. \quad (4)$$

If HQ values are near or above 1, exposure levels are near or above the exposure benchmark underlying the BE value.

3. Results and discussion

3.1. Ecological exposure assessment

The aquatic food web models included in MERLIN-Expo provided as output of the deterministic simulation the time trend of concentrations from 1924 to 1998 of all target chemicals in aquatic organisms included in the Venice lagoon food web.

Time dependent concentrations of 2,3,7,8-TCDD and PCB126 in selected species are reported in Fig. 3 and Fig. 4 respectively. Results, expressed on a fresh weight basis, show the highest accumulated concentrations for phytoplankton for 2,3,7,8-TCDD and for *T. philippinarum* (Manila clam) for PCB126. The lowest concentrations are obtained for *S. aurata* (sea bream) for 2,3,7,8-TCDD, while the species showing the lowest internal concentrations of PCB126 is *Dicentrarcus labrax* (seabass). Time dependent concentrations in biota reflect the shape of time trend of contamination in sediment and water compartment, although with appreciable differences in the magnitude of peaks depending on the specific biological and physiological characteristics of each animal and on physico-chemical characteristics of target chemicals. Despite the trend generally observed in dioxins and PCBs sediment contamination in Venice lagoon (as reported in Section 2.1), in the case at hand it is possible to notice that each considered substance follows an individual, specific trend, with peaks in specific decades, which is reflected by simulated concentrations in aquatic biota.

With the aim of obtaining a preliminary evaluation of model performance, the estimated concentrations in aquatic organisms were compared to available measurements in organisms sampled in the central lagoon area and in northern lagoon area (in the case of mullet) in 1998 (Venice Water Authority, 1999). Sampling locations and number of sampled individuals for each species are reported in Table S4 in SI. In Table 8, the comparison of measured and simulated concentrations of target chemical compounds in aquatic species is reported. Since biota samples have been collected in 1998, simulated concentrations for the same year have been selected for the comparison.

The observed bioaccumulation factor (BAF_o) has been calculated for each species and each chemical as the ratio of the measured

Table 7
Indicators of model performance for single species and for the overall model.

	Tapes philippinarum	*Carcinus mediterraneus*	*Chelon labrosus*	*Zosterisessor ophicephalus*
Model bias (MB_j) for single species	46.05	3.97	0.95	0.30
Overall model bias (MB)	12.82			

Table 8
Calculation of Hazard Quotient for *C. labrosus* and *Z. ophiocephalus* considering dioxins and dioxin-like PCBs included in the ecological exposure estimation.

Chemical		*Chelon labrosus*	*Zosterissessor ophiocephalus*	*Atherina boyeri*	*Sparus aurata*	*Dicentrarcus labrax*	*Dicentrarcus labrax* juv	*Sparus aurata* juv	*Chelon labrosus* juv
		Simulated concentrations (mg/kg_{fw})							
2,3,7,8-TCDD		5.27E−08	6.42E−09	6.14E−09	2.38E−09	3.39E−09	1.27E−07	1.15E−08	1.22E−08
1,2,3,7,8-PCDD		2.80E−07	2.03E−08	2.20E−08	1.30E−08	1.88E−08	7.53E−07	3.10E−08	4.91E−08
1,2,3,4,7,8-HCDD		7.16E−07	2.65E−08	2.38E−08	2.21E−08	4.31E−08	1.39E−06	1.96E−08	6.06E−08
PCB 77		1.41E−03	4.88E−04	4.19E−04	3.47E−04	4.12E−04	3.42E−04	1.57E−04	4.73E−04
PCB 126		3.65E−05	6.78E−06	1.11E−05	8.64E−06	8.13E−06	2.63E−05	5.20E−06	1.34E−05
PCB 167		1.37E−03	1.08E−04	7.04E−05	1.09E−04	1.08E−04	5.76E−04	2.77E−05	5.76E−05
PCB 169		1.14E−05	8.90E−07	5.71E−07	9.52E−07	9.42E−07	3.69E−06	1.97E−07	5.56E−07
	WHO TEF for fish	Concentration (mg TEQ/kg_{fw})							
2,3,7,8-TCDD	1	5.27E−08	6.42E−09	6.14E−09	2.38E−09	3.39E−09	1.27E−07	1.15E−08	1.22E−08
1,2,3,7,8-PCDD	1	2.80E−07	2.03E−08	2.20E−08	1.30E−08	1.88E−08	7.53E−07	3.10E−08	4.91E−08
1,2,3,4,7,8-HCDD	0.5	3.58E−07	1.33E−08	1.19E−08	1.10E−08	2.16E−08	6.97E−07	9.81E−09	3.03E−08
PCB 77	0.0001	1.41E−07	4.88E−08	4.19E−08	3.47E−08	4.12E−08	3.42E−08	1.57E−08	4.73E−08
PCB 126	0005	1.83E−07	3.39E−08	5.56E−08	4.32E−08	4.06E−08	1.31E−07	2.60E−08	6.68E−08
PCB 167	0.000005	6.86E−09	5.39E−10	3.52E−10	5.46E−10	5.41E−10	2.88E−09	1.39E−10	2.88E−10
PCB 169	0.000005	5.71E−11	4.45E−12	2.85E−12	4.76E−12	4.71E−12	1.84E−11	9.86E−13	2.78E−12
SUM TEQ		1.02E−06	1.23E−07	1.38E−07	1.05E−07	1.26E−07	1.74E−06	9.42E−08	2.06E−07
HQ		0.16	0.02	0.02	0.02	0.02	0.27	0.01	0.03

concentration in the organism and the corresponding concentration in water, while the predicted bioaccumulation factor (BAF_p) has been calculated as the ratio of the simulated concentration in the organism and the corresponding chemical concentration in water. Fig. 5 shows observed versus predicted logBAFs for all target chemicals and for *T. philippinarum*, *C. mediterraneus*, *C. labrosus* and *Z. ophiocephalus*.

The performance of the food web bioaccumulation models was evaluated according to the approach described in Section 2.5. The calculated model bias indicators for each species and the overall model bias are reported in Table 7.

From the results reported in Table 6 and Table 7 and from Fig. 5 it is possible to observe that the model overestimates of at least one order of magnitude chemical concentrations, and accordingly logBAF, for the species *T. philippinarum* for all considered chemicals. This is confirmed by a high value of the model bias estimated for this species. It is worth mentioning that the sampling site where clams were collected were not identical to the sampling site of the considered sediment core. Since clams are sessile organisms (not moving across different areas as fish species), the distance between sediment and biota samples might affect significantly the comparability of modelling and monitoring concentrations. It was therefore decided to test the model on an additional set of data, including sediment concentrations (surficial sediment, first 15 cm) and clam concentrations in the same location from the same monitoring campaign, considering only one time point for 2003 (data available from ICSEL project, 2003). Results are reported in Table S5 in SI, from which it can be noticed that the difference between measured and monitored data improved if compared with 1998 data. Anyway, an overestimation of model predictions in comparison with measurement data can still be observed for *T. philippinarum*: further testing of the model on more extended datasets (from both temporal and spatial perspective) can help in understanding better the behaviour of the Invertebrate model for filter feeder organisms under different scenarios and support the identification of possible adjustments to improve its capability of approximate real bioaccumulation measurements.

At the same time, it is possible to observe that results obtained for other species are encouraging and turn out to be quite consistent with measured concentrations in biota samples, with differences depending on the species and the individual chemical. This is particularly true in the case of *C. labrosus*, for which the estimated model bias achieves a value of 0,95, therefore quite close to the target value of 1 (Table 7).

An evaluation of ecological exposure estimates has been performed for fish species according to the approach described in Section 2.6. Results for all fish species included in the simulated food web are reported in Table 8. It can be observed that the highest HQ is estimated for juveniles of *D. labrax* (equal to 0.27), but in general for all considered species the estimated HQ is below 1, meaning that no potential adverse effects for the considered species are expected as a consequence of the exposure to the two investigated contaminants.

3.2. Human exposure assessment

Taking into account the available human biomonitoring data, MERLIN-Expo has been applied to simulate lifetime internal exposure to 2,3,7,8-TCDD and PCB126 for a group of men classified as “high fish consumers” and born between 1924 and 1972 (Frangipane, 1999; see Section 2.1). For this assessment, the full chain of models illustrated in Section 2.2 has been applied. The final outputs of interest provided by the Man model consist of time-dependent chemical concentrations in different human tissues and organs (e.g., blood, adipose tissue, brain, liver), but it is important to remind that MERLIN-Expo can provide additional intermediate outputs (e.g., total quantity of chemical ingested through the dietary pathway at different ages, quantity of chemicals excreted or metabolised by the organism at different time), which can support the understanding of exposure pathways and toxico-kinetic processes.

Fig. 6 shows the changing lifetime concentrations of 2,3,7,8-TCDD in human blood for selected individuals born between 1924 and 1972, accompanied (in order to support interpretation of results) by time trends of chemical concentrations in sediment and water from 1924 to 1998

Table 9
Comparison of different statistics for simulated and measured values of 2,3,7,8-TCDD and PCB126 in human blood (mg/L) of high fish consumers (22 persons).

		Mean	SD	Min	Max	Geometric mean	Geom SD	Median
2,3,7,8-TCDD	Measured	9.06E−09	8.92E−09	1.28E−09	2.95E−08	4.98E−09	3.16E+00	4.60E−09
	Simulated	1.57E−08	5.71E−09	1.12E−08	2.57E−08	1.48E−08	1.40E+00	1.20E−08
PCB126	Measured	1.12E−06	1.13E−06	1.39E−07	3.97E−06	6.79E−07	2.73E+00	4.68E−07
	Simulated	7.60E−08	3.04E−09	6.63E−08	7.73E−08	7.60E−08	1.04E+00	7.70E−08

Table 10
Evaluation of internal exposure estimates of 2,3,7,8-TCDD and PCB126 obtained by MERLIN-Expo against Biomonitoring Equivalent for dioxin TEQ.

Dioxin TEQs estimated for 22 high fish consumers (sum of 2,3,7,8-TCDD and PCB126) — pg/g serum lipid				
	Mean	Geometric mean	95th percentile	Biomonitoring Equivalent (BE)
	4.56	4.22	7.69	21
HQ	0.22	0.20	0.37	

used as input to the model chain (i.e., inputs to aquatic food web models). Fig. 7 illustrates the same results and data for PCB126.

In general, the trend in environmental concentrations is in some way reflected into human internal exposure values, but it is "modulated" by absorption, distribution, metabolism and elimination processes regulated by chemical-specific characteristics (such as K_{ow} and metabolic half-life).

The chart in Fig. 6 shows that individuals born after 1956 tend to have lower blood concentrations of 2,3,7,8-TCDD than individuals born before 1951. Body burden of PCBs and dioxins has been shown to increase with age (e.g., Hardell et al., 2010; Sweetman et al., 2000) but this is not the only factor significantly affecting the overall burden. From Fig. 6 it is possible to conclude that trends in 2,3,7,8-TCDD concentrations in blood are not only related to the age of individuals but rather reflect a time-dependent chemical input profile, obtained as a combination of changing environmental (and food web) contamination and age-dependent dietary intakes.

As for PCB126, lifetime concentrations illustrated in Fig. 7 show a similar trend for all individuals, in most cases with a peak of different magnitude (depending on the year of birth) in the first years of life, followed by an overall decrease. These early life peaks can be observed also for 2,3,7,8-TCDD, even if in this latter case they are less evident. These peaks cannot be explained only by a higher level of food contamination, because they are visible also when simulations with constant environmental concentrations over lifetime are run (a test was performed, without changing the values of other input data). These peaks can be associated to the use of an average daily intake of fish and seafood for children between 1 and 9 years, according to the available food intake statistics. This low resolution in intake rates for toddlers combined with the low weight in early life stages can explain the observed peaks and suggests a refinement of intake input data for young population groups whenever possible.

With the aim of performing a verification of model performance in reconstructing human internal exposure, simulated results have been compared to the available human biomonitoring data, i.e., concentrations of PCB126 and 2,3,7,8-TCDD in blood serum of 22 adult males living in Venice municipality and classified as "high fish consumers". Since MERLIN-Expo provides concentrations of target chemicals in whole blood as output of the Man model, measured concentrations in serum have been properly transformed into equivalent concentrations in blood. Considering that in the case of PCBs and dioxins a significant fraction of chemical tends to distribute in blood serum (Schecter, 2012), the concentration in blood has been assumed half of the concentration in serum, as recommended by Health Canada (Tsuji et al., 2005) for PCBs.

In general, the comparison between human biomonitoring data and simulated blood concentrations is not straightforward because cross-sectional data generated through biomonitoring studies are based on group of individuals sampled at the same time, while longitudinal estimates provided by MERLIN-Expo represent single individual over their whole lifetimes. Available biomonitoring data have been compared with the simulated concentrations (22 persons) for year 1998. In Table 9 the comparison of statistics for measured and modelled blood concentrations of 2,3,7,8-TCDD and PCB126 is reported. Available biomonitoring data for PCB126 follow a lognormal distribution, while 2,3,7,8-TCDD concentrations do not follow neither lognormal nor normal distribution (and a significant number of values was below the detection limit), therefore for sake of completeness in Table 9 different statistics are reported.

As an overall outcome, it can be observed that simulated data are in a relatively good agreement with measured data obtained from 1998

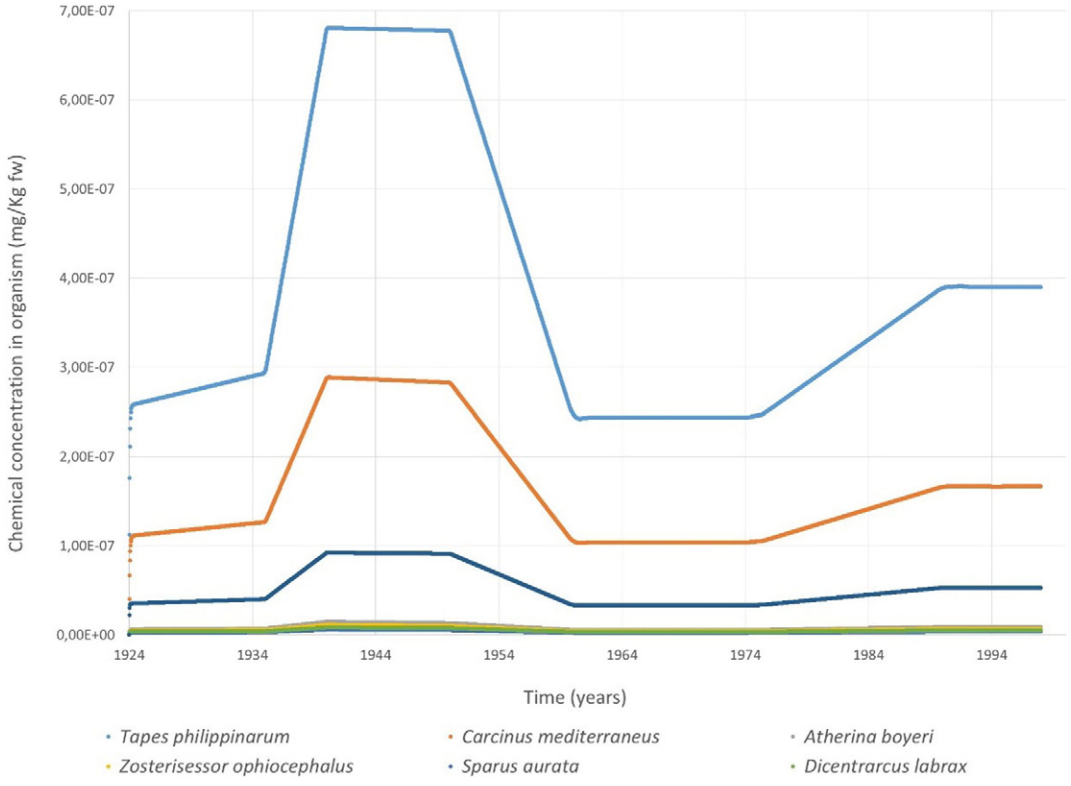

Fig. 3. Modelled concentrations of 2,3,7,8-TCDD in selected organisms of the Venice aquatic food web.

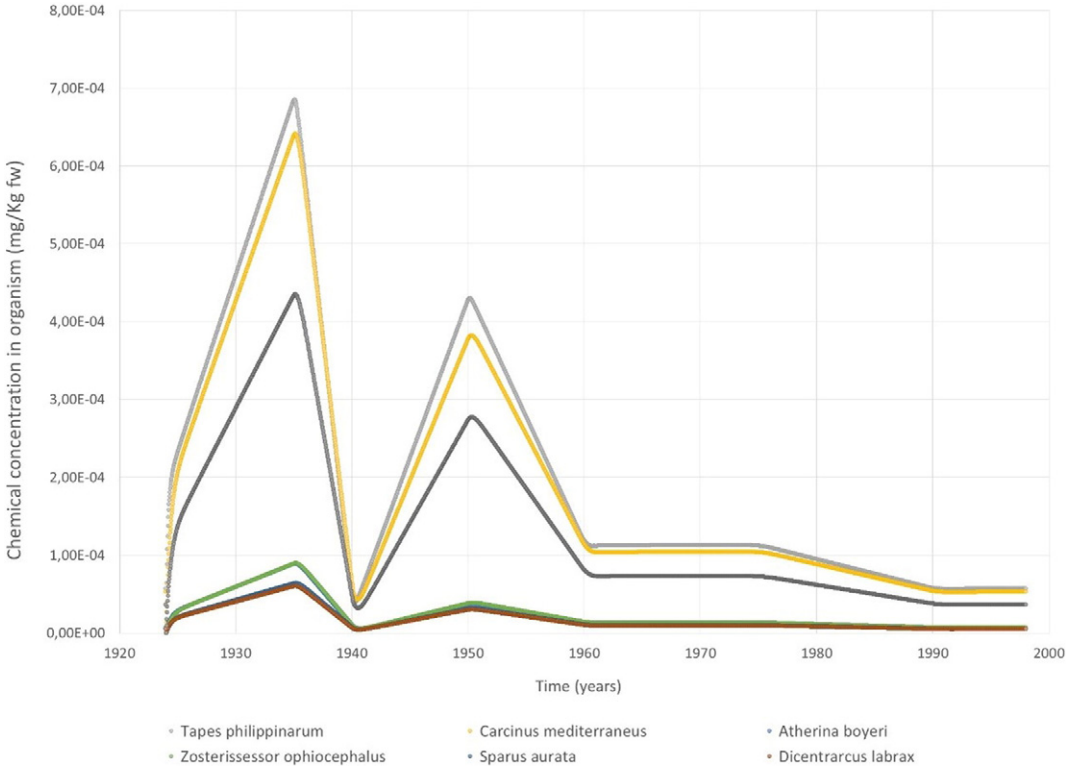

Fig. 4. Modelled concentrations of PCB126 in selected organisms of Venice lagoon food web.

survey in Venice municipality from high fish consumers. Measured and simulated data have similar orders of magnitude, the geometric mean (GM) of simulated 2,3,7,8-TCDD values in blood is about three times the GM of measured values, while for PCB126 the geometric mean of simulated values is one order of magnitude lower than GM of measured data.

It is noteworthy to remind the assumptions related to the assessment framework, which play a relevant role in influencing modelling results and have to be considered in their evaluation. First, a worst-case scenario was adopted in the assessment, where it is assumed that all fish and seafood consumed by the population are caught in a very contaminated area of the lagoon, very close to industrial emission

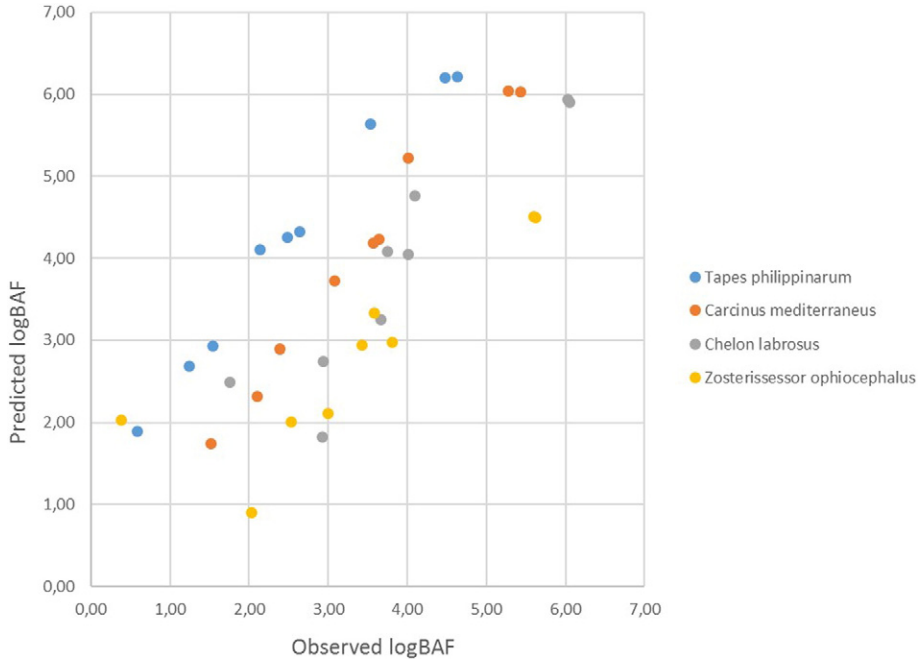

Fig. 5. Observed versus predicted log bioaccumulation factors (logBAF) for the target chemicals for the species *Tapes philippinarum*, *Carcinus mediterraneus*, *Chelon labrosus* and *Zosterisessor ophiocephalus*.

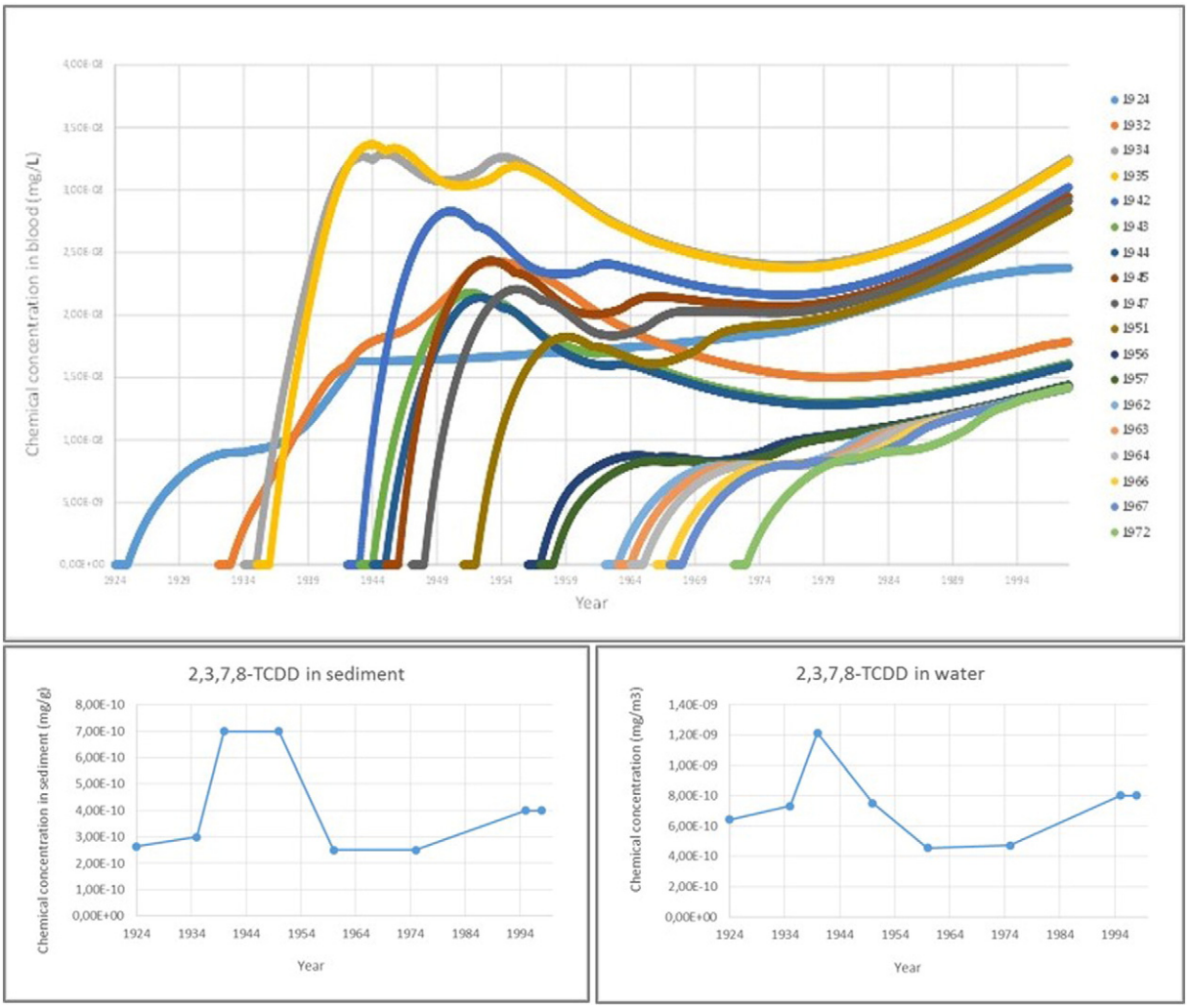

Fig. 6. Lifetime concentrations of 2,3,7,8-TCDD in blood of high fish consumers born between 1924 and 1972.

sources. This worst-case assumption helps in exploring the upper bound of human exposure to target chemicals, but it also leads to an overestimation of blood concentrations in comparison with realistic exposure conditions (i.e., fish and seafood from different sources and probably from less contaminated areas, especially after the ban of fishing activities in front of Porto Marghera in the 1990s). At the same time, the contribution to chemical exposure from other food items such as meat or dietary products was not considered in the assessment. Even if fish and seafood can probably be considered among the most relevant sources of TCDD and PCB126 in the diet for high fish consumers, the exclusion of other dietary sources likely leads to an underestimation of internal exposure. Finally, it has to be considered that in the reconstruction of human exposure, only average value of daily intakes of fish and seafood for different age groups were used, since quantitative data on daily consumption of different food types were not available for each participant. This condition hampers the comparison of data at the individual level, because the model provides identical results for all individuals born in the same year if other parameters, such as food intake rates, are not varied.

Internal exposure estimates obtained from MERLIN-Expo application have been evaluated according to the approach described in Section 2.6.

Blood concentrations (mg/L) of 2,3,7,8-TCDD and PCB126 obtained by MERLIN-Expo simulation for individual high-fish consumers were converted into lipid-adjusted serum concentration by multiplying for a factor of two (blood to serum concentration conversion according to Health Canada, 2003) and by adjusting for the total lipid concentration of individual serum samples as reported by Frangipane (1999). TEQs concentration of PCB126 were obtained by multiplying the concentrations by PCB126 TEF, defined as equal to 0.01 for humans (WHO, 2005).

Table 10 provides a comparison of statistical values for the internal exposure estimates calculated by MERLIN-Expo with the selected BE. It can be noticed that HQ values are all below the value of 1, even in the case of the 95th percentile. However, it is important to remind that the HQ is calculated only taking into account two chemicals, 2,3,7,8-TCDD and PCB126, therefore the inclusion of other dioxins and other dioxin-like PCB congeners in the assessment might lead to higher values.

4. Conclusion

The new exposure modelling tool MERLIN-Expo was applied to assess the bioaccumulation and biomagnification of a set of dioxins and PCBs in the aquatic food web of the Venice lagoon and the exposure of local population (high fish consumers sub-group) through the intake of contaminated seafood from the same lagoon. For these purposes, five models from MERLIN-Expo library were combined (Phytoplankton, Invertebrate, Fish, Human Intake and Man models) and deterministic simulations were run for a time period of several decades, from 1924 to 1998. For the

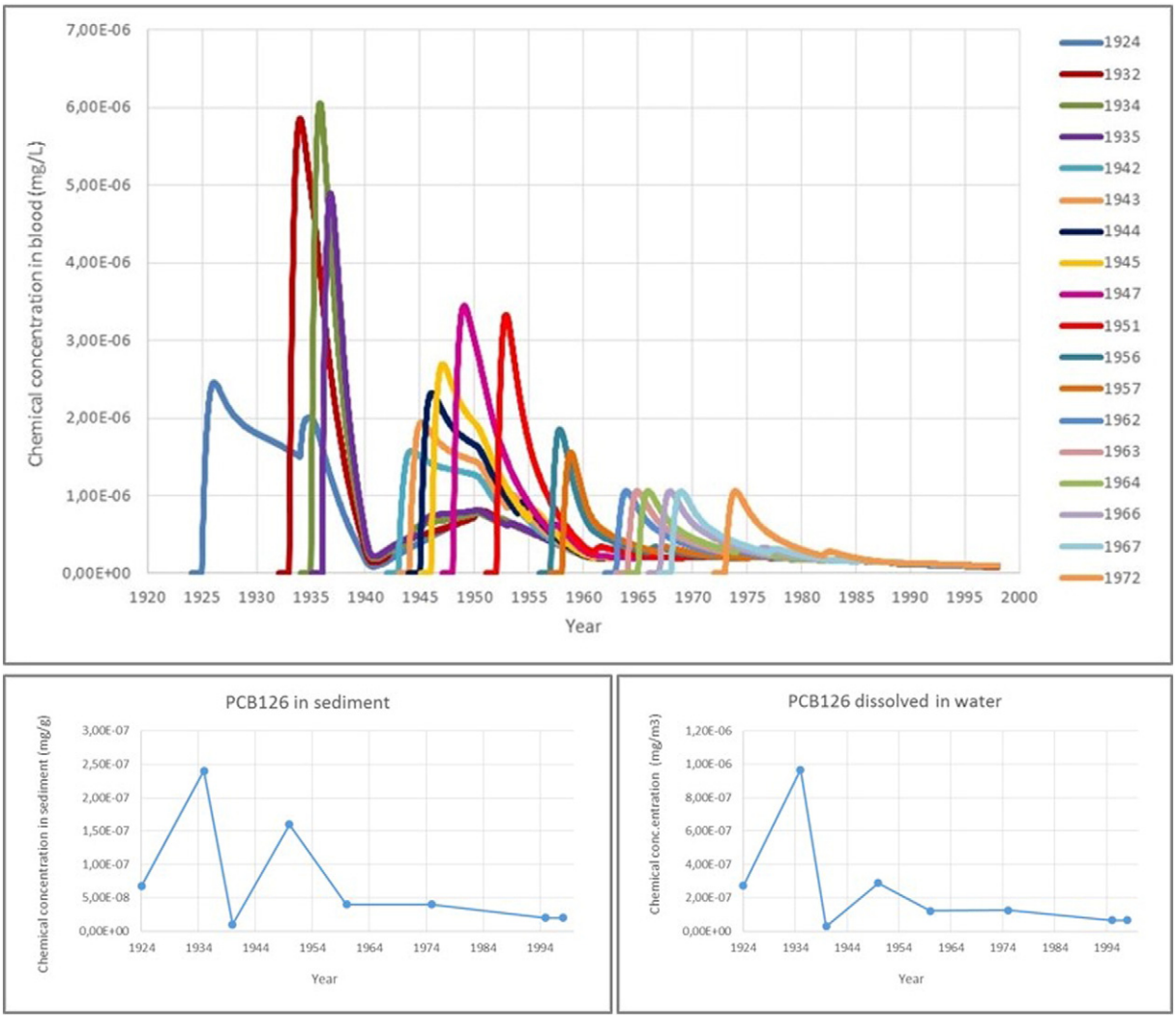

Fig. 7. Lifetime concentration of PCB126 in blood of high fish consumers born between 1924 and 1972.

considered classes of chemicals, the application demonstrated the feasibility of reconstructing with MERLIN-Expo detailed long-term exposure scenarios addressing both ecological and human exposure issues and considering different targets. The flexibility of the modular structure of MERLIN-Expo allowed reconstructing a rather complex aquatic food web, representative of Venice lagoon ecosystem and including 17 different aquatic species. Moreover, simulated concentrations in edible species were used, together with age dependent food intake rates, to reconstruct human internal exposure for local population subgroup (adult males, high fish consumers). The ecological exposure assessment targeted different congeners of PCBs and dioxins, demonstrating the possibility to run simulations for several contaminants at the same time. This feature allows to easily compare the behaviour of chemicals with different physico-chemical characteristics and to explore their potential for bioaccumulation and/or bio-magnification in a straightforward way. MERLIN-Expo proved to be flexible and suitable to support integrated exposure assessment of dioxins and PCBs where both ecological and human targets are considered, even for long term scenarios, and the model performance, evaluated against real monitoring data, are satisfying if all the assumptions included in the assessment framework are considered.

Despite the uncertainties associated with the assessment framework and data availability and treatment (e.g., reconstruction of water concentrations, interpolation, blood to serum transformation), the results of the described application can already show how MERLIN-Expo can be used, for PCBs and dioxins, to reconstruct real biomonitoring data with a good approximation (comparable orders of magnitude between simulated and measured concentrations in blood). As a further development of this work, a more refined characterization of exposure scenarios could be carried out in order to make the predicted results and the biomonitoring data fully comparable and provide a quantitative evaluation of modelling performance.

In the application described in this paper, MERLIN-Expo proved to be promising as a useful tool for detailed assessment of exposure in higher tier risk assessment procedures, to complement or support the interpretation of existing monitoring data or to explore future exposure scenarios, and it is advisable to test these potentialities for other classes of chemicals which can be analysed with these tool (e.g., PAHs, phthalates, pesticides, metals).

For the Venice lagoon case study, the results obtained from MERLIN-Expo application allowed to perform a preliminary ecological and human health risk assessment for the considered chemicals, by comparing the internal exposure estimates against existing benchmark values available in literature. No conditions of significant ecological or health risk have been detected for the considered worst-case scenario, however it is important to remind that the case study application included only a very restricted set of target chemicals and exposure pathways and it would be relevant to extend the application to other substances with similar modes of action in order to perform a full risk assessment for

local ecosystem and human population. Moreover, the consideration of different and more complete exposure scenarios would allow to better explore the implications of changes in environmental contamination and exposure parameters (such as diet habits) on the overall exposure.

The uncertainties associated with the presented exposure assessment in the Venice lagoon should be properly identified and assessed, with the aim of quantifying the margin of variability of the model outputs attributable to uncertainty and variability in input parameters. A sensitivity analysis is surely beneficial to identify the role played by different types of parameters on final exposure estimates and to understand how to improve the reliability of these estimates in the proposed modelling framework. These aspects are presented in detail in a companion paper in this issue (Radomyski et al., this issue).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2016.04.146.

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