User Blood and Organs Pesticides Concentration Estimation System Based on Two Compartments Parmacokinetic Models

Umberto Cerasani
CERAGOS Electronics and Nature
Sophia Antipolis, France
Email:cerasani@ceragos.org

Dominique Bedra
CERAGOS Electronics and Nature
Sophia Antipolis, France

***Abstract*—Pesticides are omnipresent in foods and drinks and their toxic effects are becoming evident, as well as their correlation with many diseases. Pesticides intoxication estimation could lead to lifestyle modification before certain disease symptoms occurrence. User centered application for pesticides blood and tissues concentration is proposed in this document, based on location, profession, mean food consumption and personal lifestyle indications. Three different mathematical PBPK models are used to create such system and parametrized from user personal data. User blood and tissues concentration of organophosphates per day or per year are speculated and indicated to the user.**

***Keywords*—Mathematical models; Pesticides; Pharmacokinetic modeling; user centerd application**

I. INTRODUCTION

The Food and Agriculture Organization (FAO) defines a pesticide as: "any substance or mixture intended for preventing, destroying or controlling any pest, including vectors of human or animal disease, unwanted species of plants or animals causing harm during or otherwise interfering with the production, processing, storage or marketing of food […]" [1].

In 2006 and 2007, approximately 2.4 billion kilograms of pesticides were utilized in the United States, comprising mainly herbicides (40%), followed by insecticides (17%) and fungicides (10%). The same year, more than 1,055 active ingredients were registered as pesticides [1][2].

Many pesticides can be grouped into chemical families and target organism families. Plant-derived pesticides mainly include the pyrethroids, rotenoids, nicotinoids, strychnine and scilliroside. Prominent insecticide families comprising organochlorines, organophosphates, and carbamates. Organochlorine hydrocarbons (such as DDT) could be further classified into dichlorodiphenylethanes, cyclodiene compounds, and other related compounds. Prominent families of herbicides include phenoxy and benzoic acid herbicides, triazines, ureas, and Chloroacetanilides [3].

It is estimated that over 98% of sprayed insecticides and 95% of herbicides undergoes pesticide drift since air suspended pesticides are carried out to unwanted areas [4] [6]. Pesticides are one main cause of water pollution because most of currently used pesticides are Persistent Organic Pollutants (POP) and contribute to long lasting soil contamination [7]. Their toxicities vary greatly, as well as their persistence and potential to bio-accumulate [8][11].

In certain endemic areas, pesticides are used to kill mosquitoes that can transmit potentially deadly diseases like Malaria and can protect animals from deadly parasites [2][12]. Pesticides therefore provide variety of benefits in agriculture, although there are multiple undesirable and unwanted effects of pesticide usage that are now becoming apparent. In industrialized world, most of the pesticides contamination occurs in long term and low level exposure except for few directly exposed agricultural or manufacturing workers who suffer long-term high-level exposure or less frequently acute poisoning, whereas in the countries of the developing world, the situation is almost reversed [13].

Pesticides health effects, which can be acute or delayed, are difficult to characterize since they interact with a plethora of enzymes, proteins, receptors and transcription factors [14].

Countless studies demonstrate the detrimental impact of pesticides in human health. Many organophosphate pesticides are potent nerve agents, functioning by inhibiting the action of acetylcholinesterase (AChE) in nerve cells and have been linked to increased Parkinson's disease occurrence and may explain increased autism frequency rate in developed countries [15][17][18]. Several pesticides have been documented to affect the endocrine system from synthesis to hormone receptor binding, acting as Endocrine Disrupting Chemicals (EDC) [14]. Pesticides such as atrazine have hazardous impact on reproductive system and fetus development and have been shown to emasculate three-quarters of exposed male frogs [19][21]. Furthermore a growing number of epidemiological and molecular studies provide substantial evidence that the pesticides are

 ISBN: 978-1-61208-502-9

associated with increased cancer risk [22]. Analyzes presented in [23] provide additional evidence for a causative relation between Pendimethalin, Dieldrin, and Parathion use and lung cancer risk. Pesticides are recognized carcinogenic for several cancers including prostate cancer, non-Hodgkin lymphoma, leukemia, multiple myeloma, and breast cancer [24]. Monitoring or estimating blood and tissues pesticides levels is hence of capital importance to prevent or cure an important number of prevalent diseases.

Quantitative Structure Activity Relationships (QSARs), are mathematical models, mostly based on Multiple Linear Regression or Partial Least Square algorithms, that attempt to relate the structure-derived features of a compound to its biological or physicochemical activity [25][26]. Although efficiently assessing acute toxicity risk linked to a chemical, chronic toxicity presents a challenge for QSAR modelling, which should ideally focus on groups of chemicals with a common mode of action [27].

Physiologically Based Pharmaco-Kinetic (PBPK) models consist of a series of mathematical representations simulating the Absorption, Distribution, Metabolism, and Excretion (ADME) of chemicals that enter the body. PBPK models utilize experimentally accepted physiological and biochemical data to predict concentrations of chemical at target tissues or organs for a wide variety of exposure scenarios [28].

PBPK rather than QSAR models have emerged as satisfactory computational approach supporting quantitative risk assessment of agrochemicals [29]. Rat study based on radiolabeled Oxadiazin and Thiamethoxan injection showed that one compartment PBPK model fits best [30]. Population Pharmacokinetic Analysis of Paraquat in Mice Following a Single Paraquat Oral Dose was performed in [31]. Cumulative risk assessment for organophosphate pesticide using PBPK model is reported in [32]. PBPK modeling was used to predict the total dose of Chlorpyrifos received by an individual from urinary biomarker measurements [33]. Since Animal studies suggest that Atrazine overexposure causes Parkinson Disease like dopaminergic toxicities, new PBPK models of Atrazine rodents exposure across the lifespan have been successfully developed [34]. Because recent exposures of organophosphate pesticides have shifted from multipathways to dietary ingestion only, modification of PBPK model input data is central to correct risk assessment and data validation [35].

In this paper, we aim to construct a system estimating user blood and other tissues pesticides levels following different types of exposure, using a two compartments PBPK model. Based on user location, job and data, a valuation of pesticides blood and tissues levels per year is proposed and near future pesticides body internal levels could be extrapolated.

The first section of this document presents the general principle of the user based system developed, the second section introduces the theoretical basis of our model construction, mostly based on drugs pharmacokinetic mathematical models. The following section describes the corresponding results obtained from experimentally defined parameters. A final discussion concludes this paper, presenting the theoretical benefits and limitation of this proposed modeling work.

II. USER CENTERED SYSTEM OF INFORMATION

Estimating blood and other tissue pesticides is very challenging, partial, limited to a few compounds and most of the time highly speculative or inexact. We aimed to create an innovative program based on a few samples.

User location once correlated to pesticides estimation maps per countries area which are available for certain regions, allowed to assess user exposure levels to water and air pesticides. The amount of food consumed per week and the quality of it is also a capital information helping to determine personal user pesticides exposure. We further develop 3 different PBPK models which were selected from user profession and location and corresponding to (1) low levels long lasting exposure (all population group), (2) middle to high levels long lasting exposure (pesticides manufacturer, user close to large agricultural fields, etc.), (3) very elevated models of exposure in a short time (pesticides poisoning corresponding to farmer pesticides dissemination periods, etc.). Finally, user lifestyle general data were also taken into consideration, such as the amount of sport per week since sweating may help in pesticides elimination for instance.

Our program uses these values as parameters which were injected into different mathematical models to finally inform the user of its mean exposure exposition every day and user specific pesticides accumulation per year are speculated.

Two types of user based systems are currently being developed: (1) the first requires user connection to an interactive website, (2) the second system is a smartphone apps, requiring the same user informative procedure and connecting to the same processing center address were computations are made. Then, user pesticides accumulation assessment are reported to the user, associated with general population statistics. Both systems are introduced in Figure 1.

 ISBN: 978-1-61208-502-9

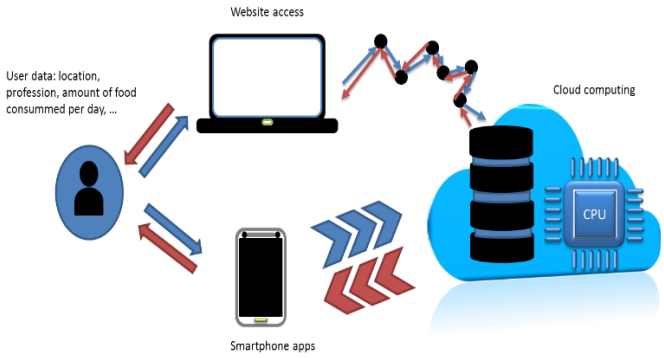

Figure 1. CENTRIC based system for user pesticides estimation

III. METHODOLOGY AND MODEL PARAMETERS

Compartment models theoretical basis are generally described in [36][37][38]. They aim to characterize the dynamics of state variables in various volumes referred as compartments. PBPK drugs studies permit to characterize the dose-concentration-effect/toxicity relationship, evaluates the drug/disease interactions and simulate the drug responses in various organs [39]. Although very complex and multi-compartments models exist for drugs predictive evaluation [40], intervening in drug product development, analysis of pesticides dynamics once introduced in the body are less numerous [35][37][41][43].

The two compartments PBPK model was preferred since single compartment model does not correctly model pesticides accumulation in tissues and because pesticides blood concentration often involves two distinct biological half-live: one associated with rapid plasma removal and the other with long lasting pesticides accumulation in tissues [44]. Obviously, more complex PBPK models could have been used, permitting to more efficiently correlates pesticides accumulation in certain tissues and associated diseases occurrence, but pesticides distribution in tissues is insufficiently characterized in current literature. For instance, our model does not include permanent body pesticides stores which may be the case in real world such as bones or brain accumulation pools.

Various pesticides kinetics experiments, mostly based on rats are reported in Table I, corresponding to the [31][34] [45][46] results. Performing interspecies results extrapolation of most of the parameters involved was proven acceptable according to [47] and parameters determined from rats experiments can be directly applied to humans by modifying only the body weight.

Since the pesticides containing the organophosphates Parathion and Diazinon individuate the parameters needed for the two compartment PBPK model adaptation to pesticides, we chose to restrict our models to organophosphates Parathion and Diazinon only. The conclusion for other pesticides may vary greatly since the molecules involved could be totally different as their metabolism in the human body. Besides, in the result section we report pesticides models conclusions only based on Parathion and Diazinon pesticides dynamics and much diverse results may be obtained from different pesticides type.

The two compartments PBPK model we used in described in Figure 2, where K_a represents the absorption rate, K_e the elimination rate, K_c and K_d the inter-compartment exchange rate and K_m the metabolic rate of the Peripheral Compartment (PC). We neglected K_m in the first place although specific metabolic models such as Michaelis Menten could have been used [48][50]. The volume of the Central Compartment (CC) is referred as V_c which includes highly irrigated and poorly storing pesticides organs as well as plasma whereas V_p represents the volume of pesticides internalizing organs.

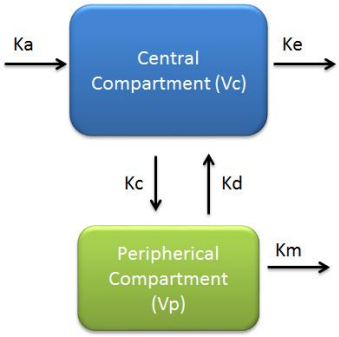

Figure 2. Two compartment pharmacokinetic model used for tissue drug repartition and evolution

A. *Mathematical PBPK models of intravenous injection:*

According to the two compartments PBPK model, we suppose that the toxins concentration ($C_c(t)$) in the Central Compartment (CC) is described by (1):

$$C_c(t) = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

where $Ae^{-\alpha t}$ models the distribution phase of the organophosphates from the CC to the PC or the amount of organophosphates directly excreted. In contrast $Be^{-\beta t}$ models the elimination phase where both CC and PC excrete the pesticides accumulated.

The mathematical expression presented here corresponds to an intravenous injection of the organophosphates without PC metabolic activity ($K_a = 0$ and $K_m = 0$).

Defining $m_c(t)$ the mass of pesticides in the CC and $m_p(t)$ the mass of pesticides in the PC and applying the mass conservation principle, we obtain (2):

 ISBN: 978-1-61208-502-9

$$(S_1)\begin{cases}\dfrac{dm_c(t)}{dt} = (-K_e - K_C) * m_c(t) + K_d * m_p(t) \\ \dfrac{dm_p(t)}{dt} = K_c * m_c(t) - K_d * m_p(t)\end{cases} \quad (2)$$
$$\rightarrow \begin{cases} m_c(t) = r * e^{\lambda_1 t} + s * e^{\lambda_2 t} \\ m_p(t) = v * e^{\lambda_1 t} + w * e^{\lambda_2 t}\end{cases}$$

λ_1, λ_2 are the eigenvalues of the matrix $M = \begin{pmatrix} -K_e - K_C & K_d \\ K_c & -K_d \end{pmatrix}$, (r, s, v, w) can be find using the initials conditions, which are identified with experimental measures. Besides, inserting the volume of distribution, permits to relate the toxin mass in the CC with its concentration in this compartment, as described by (3):

$$\frac{m_c(t)}{V_c} = C_c(t) \text{ with } V_c = \frac{A+B}{DOSE}$$
$$\text{and } \frac{m_p(t)}{V_p} = C_p(t) \text{ with } V_p = V_c * \frac{K_c}{K_d} \quad (3)$$

where DOSE corresponds to the amount of pesticides injected and was fixed to 5 mg/kg of body weight for the intravenous injection model (bolus model) or to 50 mg/kg of body weight for the oral absorption model, corresponding to the values described in Table I.

The initial conditions are determined from experimental measurements ($m_c(0)$ = DOSE and $m_p(0) = 0$ since the pesticides dose in directly injected in plasma at t = 0) and were injected in the S_1 system yielding (4):

$$\begin{cases} r + s = DOSE \\ \lambda_1 * s + \lambda_2 * r = (-K_e - K_c) * (r + s) \\ v + w = 0 \\ \lambda_1 * v + \lambda_2 * w = K_c * (r + s)\end{cases} \quad (4)$$

Consequently, we obtained:

$$\begin{cases} r = \dfrac{DOSE * (K_e + K_c + \lambda_2)}{\lambda_2 - \lambda_1} \\ s = -\dfrac{DOSE * (K_e + K_c + \lambda_1)}{\lambda_2 - \lambda_1} \\ v = -\dfrac{K_c * (DOSE)}{\lambda_2 - \lambda_1} \\ w = \dfrac{K_c * (DOSE)}{\lambda_2 - \lambda_1}\end{cases} \quad (5)$$

Since $r = \frac{A}{V_c} = \frac{A*(A+B)}{DOSE}$ and $s = \frac{B}{V_c} = \frac{B*(A+B)}{DOSE}$, this leads to the system presented in (6):

$$(S_2)\begin{cases} \dfrac{A*(A+B)}{DOSE} = \dfrac{DOSE*(-K_a + K_e + K_c + \lambda_2)}{\lambda_2 - \lambda_1} \\ \dfrac{B*(A+B)}{DOSE} = -\dfrac{DOSE*(-K_a + K_e + K_c + \lambda_1)}{\lambda_2 - \lambda_1} \\ \alpha = \lambda_1 \\ \beta = \lambda_2\end{cases} \quad (6)$$

Solving S_2 permits to extract the value of K_e, K_c, K_d.

Because toxins kinetics are less well characterized than drugs kinetics, toxins body metabolism and excretion are often described by other constants such as biological half-life ($t_{1/2}$), rate of clearance (CL) and excretion rate (K_e). We should hence first find the corresponding (A, B, α, β) from ($t_{1/2}^{fast}$, $t_{1/2}^{slow}$, CL, K_e) before finding the two compartments models parameters (K_c, K_d, …)

The elimination of a drug (or a toxin) in plasma (Central Compartment) has a distribution phase (rapid phase of plasma removal because of elimination and organs accumulation) and a slow phase (only elimination from the CC and PC), two biological half-life are often reported: one attributed to the rapid phase ($t_{1/2}^{fast}$) and one to the slow phase ($t_{1/2}^{slow}$), defining the system of equation (S_3) reported in (7):

$$(S_3)\begin{cases} Ae^{-\alpha t_{1/2}^{fast}} = \dfrac{A}{2} \rightarrow t_{1/2}^{fast} = \dfrac{\ln(2)}{\alpha} \\ Be^{-\beta t_{1/2}^{slow}} = \dfrac{B}{2} \rightarrow t_{1/2}^{slow} = \dfrac{\ln(2)}{\beta} \\ CL = \dfrac{DOSE}{\int_0^{\infty}(Ae^{-\alpha t} + Be^{-\beta t})dt} = \dfrac{DOSE}{\frac{A}{\alpha} + \frac{B}{\beta}} \\ K_e = CL * \dfrac{DOSE}{A + B}\end{cases} \quad (7)$$

Knowing ($t_{1/2}^{fast}$, $t_{1/2}^{slow}$, CL, K_e) permits to numerically compute (A, B, α, β), using Maple® implementation of the (S_3) system for instance.

B. Mathematical PBPK models of oral pesticides absorption:

Injection of pesticides intravenously only serves theoretical purposes. Pesticides are absorbed by various means and greatly depends on individual location, work and general lifestyle. We chose to model three types of pesticides absorption: (1) one associated with repeated low levels of pesticides absorption (mainly oral through food and drinks contamination) and regarding all population groups, (2) another one associated with constant medium to high levels of pesticides absorption, mostly through skin and lungs and concerning very specialized workers such as pesticides manufacturers and (3) a model associated with high level and short term pesticides absorption corresponding to farmer pesticides exposition during pesticides field deposition.

Accordingly, we modify the intravenous model of pesticides absorption, injecting an input term represented by the function $T_x(t)$. Adding an input function ($T_x(t)$) to the system resulted in a permanent modification of the solution such as expressed in (8):

$$(S_3)\begin{cases} \dfrac{dm_c(t)}{dt} = (-K_e - K_C) * m_c(t) + K_d * m_p(t) \\ \qquad + K_a * T_x(t) \\ \dfrac{dm_p(t)}{dt} = K_c * m_c(t) - K_d * m_p(t)\end{cases} \quad (8)$$

 ISBN: 978-1-61208-502-9

The solution of this first order differential system of equations ($m_c(t) = r * e^{\lambda_1 t} + s * e^{\lambda_2 t}$ *and* $m_p(t) = v * e^{\lambda_1 t} + w * e^{\lambda_2 t}$) is similar to the solutions of separated second order differential equations [51][54].

Noticing that the homogeneous solutions of $m_c(t)$ and $m_p(t)$ are similar to homogeneous solution of second order differential equations. Since the two $m_c(t)$ and $m_p(t)$ solutions are mutually independent, the corresponding second order differential equation particular solution can be determined separately.

We first reconstructed the second order homogeneous differential equation generalized form leading to $m_c(t)$ and $m_p(t)$ homogeneous solutions by solving the system presented in (9):

$$(S_4)\begin{cases} a * C_1 * r * \lambda_1^2 + b * C_1 * r * \lambda_1 + c * C_1 * r = 0 \\ a * C_2 * r * \lambda_2^2 + b * C_2 * r * \lambda_2 + c * C_2 * r = 0 \end{cases} \quad (9)$$

Fixing a = 1 to obtain the same number of equations and unknowns, resulted in:

$$\rightarrow \begin{cases} b = -(\lambda_1 + \lambda_2) \\ c = \lambda_1 * \lambda_2 \end{cases} \quad (10)$$

Therefore, the second homogeneous differential equations described in (11), also has $m_c(t) = C_1 * r * e^{\lambda_1 t} + C_2 * s * e^{\lambda_2 t}$ as (homogeneous) solution:

$$\frac{d^2 m_c(t)}{dt^2} + (-\lambda_1 - \lambda_2) * \frac{dm_c(t)}{dt} + (\lambda_1 * \lambda_2) * m_c(t) = 0 \quad (11)$$

Including the input function, leads to the differential equation governing the CC organophosphates pesticides concentration kinetics:

$$\frac{d^2 m_c(t)}{dt^2} + (-\lambda_1 - \lambda_2) * \frac{dm_c(t)}{dt} + (\lambda_1 * \lambda_2) * m_c(t) + K_a * T_x(t) = 0 \quad (12)$$

Finding the particular solution can be achieved using the method of undetermined coefficients such as indicated in [51][53][55]. We used Maple® software to obtain the particular solution for different input function ($T_x(t)$) types.

1) Constant input function:

The mathematical description of the generalized solution is presented in (13).

$$m_c(t) = C_1 * r * e^{\lambda_1 t} + C_2 * s * e^{\lambda_2 t} + \frac{K_a * T_x(t)}{\lambda_1 * \lambda_2} \quad (13)$$

It should be notified that the amount of toxins found in plasma after a long period of time exceeding biological half lives is the ratio between the amount of toxins introduced, the absorption rate and the distribution and excretion coefficients.

2) Decreasing exponential input function:

This solution is associated with acute single pesticides exposure as it may be the case in various acute pesticides poisoning cases. We chose a decreasing exponential as input function rather than a window function as we consider that withdrawal from pesticides source exposure was gradual rather than suddenly interrupted.

$$m_c(t) = C_1 * r * e^{\lambda_1 t} + C_2 * s * e^{\lambda_2 t} + \frac{K_a * P_0 * e^{-\sigma * t}}{(\lambda_2 + \sigma) * (\lambda_1 + \sigma)} \quad (14)$$

IV. MODELS IMPLEMENTATION RESULTS:

The results presented in this section arise from Maple® software implementation of the two compartments organophosphates PBPK models.

1) Intravenous injection of organophosphates

Figure 3 depicts the CC and CP respective concentration of organophosphates. The intravenous injected dose was supposed equal to 0.05 mg/kg of body weight. Human Dianizon plasma clearance (CL) capacity was fixed to 7.58 mg/L, $t_{1/2}^{\alpha}$ to 0.33mg/h, $t_{1/2}^{\beta}$ to 4.70 mg/h.

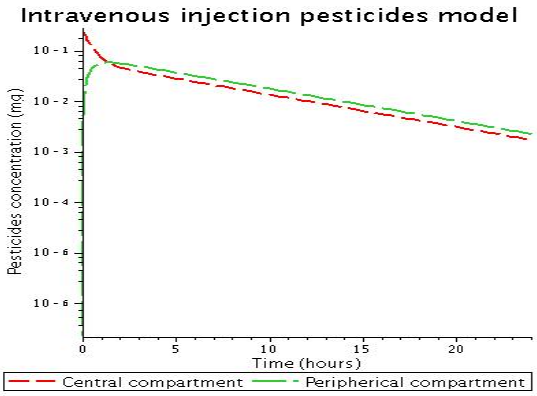

Figure 3. Bolus model of pesticides kinetic in humans

2) Oral absorption of organophosphates:

Oral absorption of a single dose of 5mg of organophosphates aimed to analyze the time needed for complete organophosphates clearance of the CC and PC. The absorption rate was based on rat gut measurements and was reported around 1.3 mg/h [45]. The other parameters were maintained similar to the intravenous model and organophosphates concentration in the CC and PC were reported in a normal and semi-log graph (Figure 4).

 ISBN: 978-1-61208-502-9

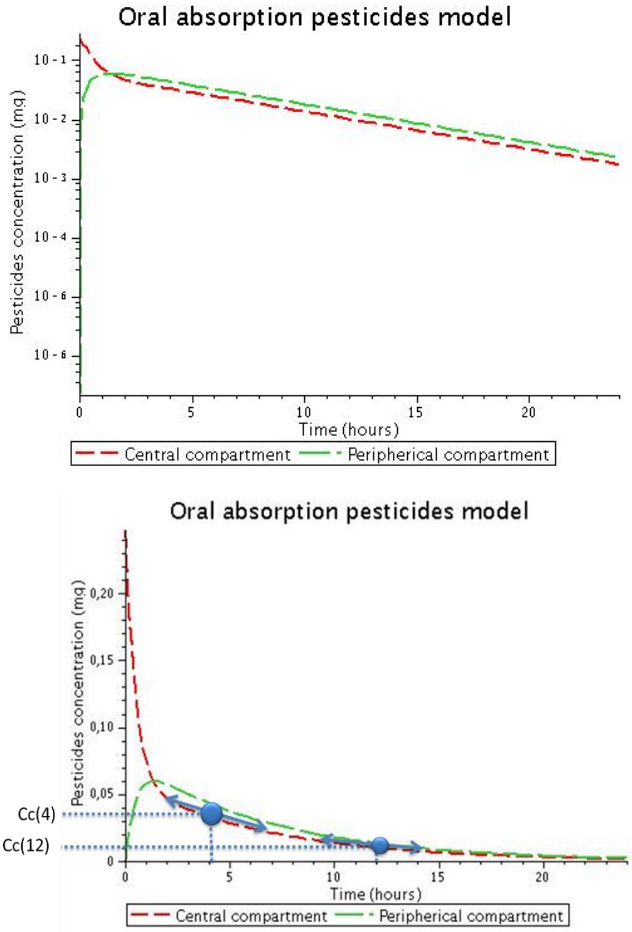

Figure 4. a. Pesticides kinetic following oral absorption in humans (semi-log plot). Figure 4. b. Pesticides kinetic following oral absorption in humans (linear plot)

3) Constant absorption of organophosphates:

The third result presented in Figure 5 corresponds to a constant absorption of organophosphates over one day, as it may be the case for individuals living near to highly concentrated pesticides field areas or pesticides manufacturer laboratory employees [56]. The absorption of pesticides is mainly performed through inhalation (K_{al}=15 L/min [57][59]) or through skin absorption (K_{as}=4.81 /cm^2/h [60][61]). We supposed that the dose constantly in contact with population in such areas was around 25 mg/day [62]. Possibly because of excretion mechanisms saturation, the CL rate was decreased (CL = 4.6 mg/L) as well as the fast and slow organophosphate biological half-live in plasma ($t_{1/2}^{\alpha}$ = 0.13 mg/h and $t_{1/2}^{\beta}$ = 1.08 mg/h).

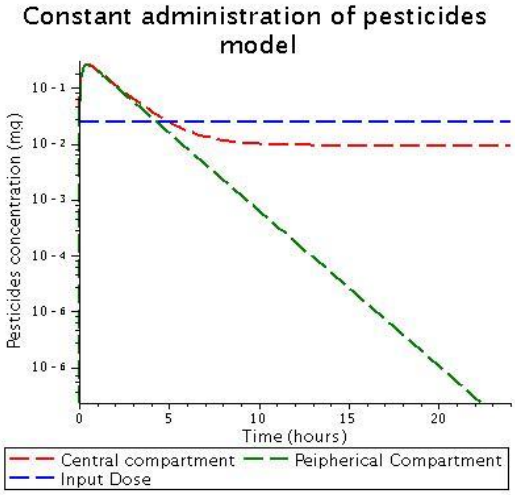

Figure 5. Constant administration of pesticides internal body stores evolution modeling workers involved in specific industries

4) Acute pesticides intoxication:

Dose response of organophosphate is presented in Figure 6 and acute pesticides intoxication is modeled in Figure 7. Pesticides absorption is often associated with inhalation or with oral route in certain cases (drinking contaminated water, etc.). The absorption function follows a decreasing exponential mathematical description since we supposed that pesticides were progressively withdrawn following intoxication. Besides this absorption function can be easily transformed into a delta Dirac function (modeling a very short term and very elevated pesticides accumulation) which has a similar mathematical description. We suppose that the absorption function was described by (15):

$$T_x(t) = P_0 e^{-\sigma * t}$$

where P_0 was fixed based on the Median Lethal Dose (LD_{50}) of values extracted from oral administration of the organophosphate Diazinon animals experiments which was reported to be around 1.250 mg/kg of body weight, meaning that from an individual of 75 kg, the LD_{50} was equal to 93 mg [62][64] and σ was arbitrarily set to 6.5 mg/h. To simplify the analysis we kept the pharmacokinetics parameters values similar to the previous case, although this might not fully depict the reality.

 ISBN: 978-1-61208-502-9

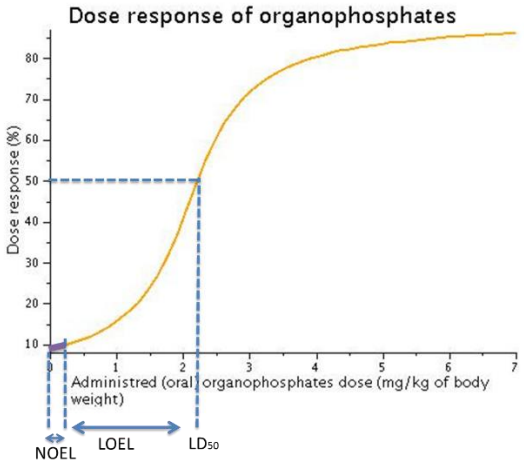

Figure 6. Dose response of specific organophosphate pesticides [62].

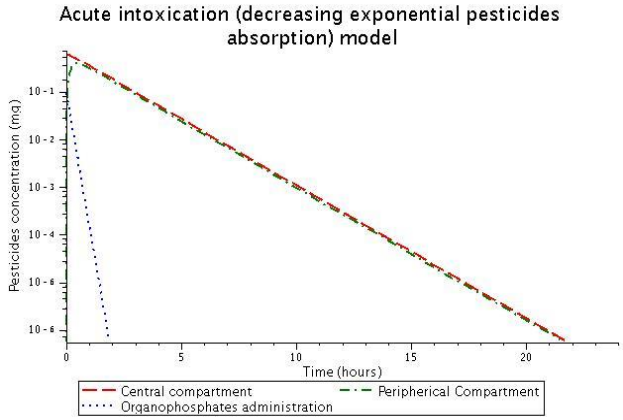

Figure 7. Acute intoxication internal body stores evolution, modeling farmer single pesticides use

5) Mean pesticides consumption over one year:

The pharmacokinetic model implementation results presented in Section III.2 permit to estimate the amount of organophosphates still in the CC and PC volumes with respect to time after oral dose administration each days. We wanted to further estimate the consumption of pesticides per individual over one year, based on the following assumptions:

- we supposed that for an average person, the main sources of pesticides intoxication is mainly from food and drinks consumption in accordance with [65][66].
- we estimated the pesticides ingested dose per day is between 2 and 10 mg based on National Estimate Daily Intakes (NEDIs) reports [67][70], although it may greatly vary depending on types of food consumed, quality of water drunk and general lifestyle.
- we supposed that each day, 4 meals were ingested, 3 of these with 3 between meals times of approximatively 4 hours and one between meals time of approximatively 12 hours (night).
- finally, we modeled the two different between meals times with Normal distributions of mean 4 and 12 (hours) and variance of 4 and 8 (hours) respectively.

Replacing the time by the Gaussian distribution values in the $C_c(t)$ and $C_p(t)$ functions , leads to the estimation of the amount of organophosphates stored per day in the CC and in the CP respectively.

Pesticides statistical daily accumulation in the various compartment is presented in Figure 8 and organophosphates accumulation estimation in one year in the CC and CP is illustrated in Figure 9 an may certainly explain disease rate explosion in industrialized countries.

V. CONCLUSION AND FUTURE WORK

In single organophosphates injection models (intravenous or through oral route), the concentration of pesticides in the Peripheral Compartment (PC) is greater than the concentration of pesticides in the Central Compartment (CC) in the distribution phase because the elimination of pesticides only occurs in the CC in this models. This may indicate that the blood concentration of pesticides does not accurately reflects the pesticides in other tissues, explaining why urine or hair analysis are sometimes preferred.

In the constant pesticide inhalation model, the final concentration of pesticides in the blood compartment is proportional to the amount of pesticides injected weighted by the ratio between the absorption rate (intestines, lungs, etc.) divided by the distribution and elimination parameters.

In the acute pesticides poisoning model, the CC and PC concentration of pesticides is maintained very elevated several hours after pesticides high exposure, most often requiring very quick and drastic detoxification measures.

Notwithstanding the two compartments PBPK model does describe pesticides storage in tissues only if K_d is neglected (Figure 2), which was not the case in our implementation. Including another compartment (representing pesticides long lasting body stores) or modifying our model could possibly lead to improved experimental data matching.

We estimated pesticides concentrated in blood and in other tissues, by extrapolating the organophosphates body kinetics. Since other pesticides may have very different kinetics and possibly much more elevated body accumulation, constructing PBPK models based on other pesticides types may help to better assess personal

 ISBN: 978-1-61208-502-9

intoxication. Ultimately pesticides biomarkers studies [57] should be confronted to our model for results validation.

Pesticides blood and tissue concentration per year for an average individual is estimated to 25 mg, which however gradually grows with respect of time. Supposing that once the pesticides concentration in a certain tissue reaches a certain threshold, tissue dysfunction is expected and disease symptoms appear, such conclusions on tissue pesticides accumulation are extremely worrying and disease occurrence is unavoidable after a certain period of time. Pesticides, because of their omnipresence in foods and drinks may hence be considered as significant etiologic factors of many diseases. Consequently, measures reducing pesticides intoxication could result in a rate regression of some deceases in industrialized countries.

Backbones for user based applications of personal blood and tissue organophosphates concentration are proposed in this document and may lead to lifestyle modification.

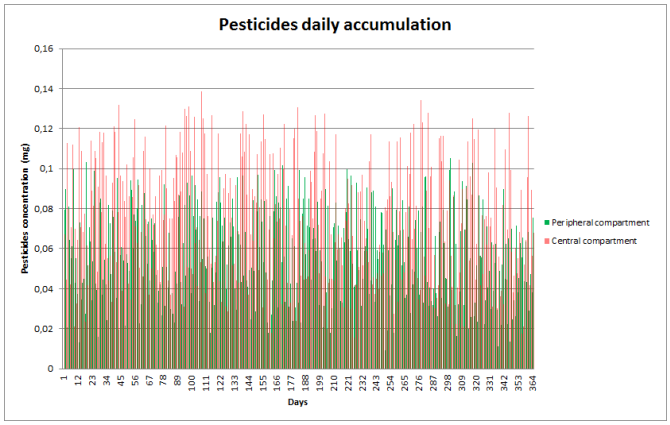

Figure 8. Pesticides daily absorption modeling of an average individual in industrialized countries

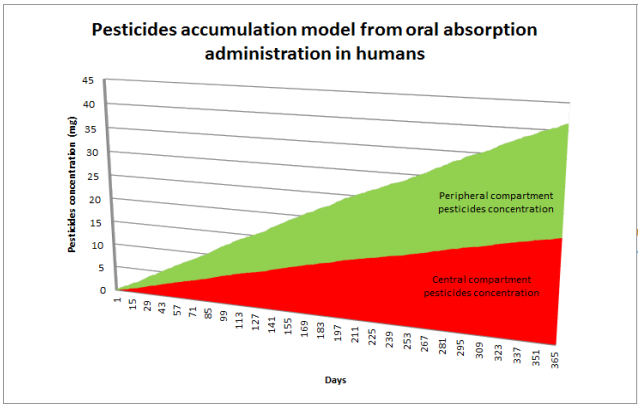

Figure 9. Pesticides accumulated in average person living in industrialized country after 1 year

REFERENCES

[1] Cdc.gov, " Pesticide Illness & Injury Surveillance - NIOSH Workplace Safety and Health Topic," 2013-09-11.

[2] G. Grullón, "Infographic: pesticide planet," *Science*, vol. 341, pp. 730-1, 2013.

[3] M. Ye, J. Beach, J. W. Martin, and A. Senthilselvan, "Occupational pesticide exposures and respiratory health," *International journal of environmental research and public health*, vol. 10, pp. 6442-6471, 2013.

[4] D. Pimentel, "Amounts of pesticides reaching target pests: environmental impacts and ethics," *Journal of Agricultural and environmental Ethics*, vol. 8, pp. 17-29, 1995.

[5] O. Zivan, M. Segal-Rosenheimer, and Y. Dubowski, "Airborne organophosphate pesticides drift in Mediterranean climate: The importance of secondary drift," *Atmospheric Environment*, vol. 127, pp. 155-162, 2016.

[6] S. Otto, D. Loddo, C. Baldoin, and G. Zanin, "Spray drift reduction techniques for vineyards in fragmented landscapes," *Journal of environmental management*, vol. 162, pp. 290-298, 2015.

[7] S. Jakuboski, "The Dangers of Pesticides," *Nature Scitable*, 201, July 25

[8] C. O. Ribeiro, Y. Vollaire, A. Sanchez-Chardi, and H. Roche, "Bioaccumulation and the effects of organochlorine pesticides, PAH and heavy metals in the Eel (Anguilla anguilla) at the Camargue Nature Reserve, France," *Aquatic Toxicology*, vol. 74, pp. 53-69, 2005.

[9] S. K. Traore *et al.*, "Contrôle des pesticides organochlorés dans le lait et produits laitiers: Bioaccumulation et risques d'exposition," *Afrique Science: Revue Internationale des Sciences et Technologie*, vol. 4, pp. 87-98, 2016.

[10] T. Katagi, "Bioconcentration, bioaccumulation, and metabolism of pesticides in aquatic organisms," in *Reviews of environmental contamination and toxicology*, ed: Springer, pp. 1-132, 2010,

[11] A. Chopra, M. K. Sharma, and S. Chamoli, "Bioaccumulation of organochlorine pesticides in aquatic system—an overview," *Environmental monitoring and assessment*, vol. 173, pp. 905-916, 2011.

[12] F. Whitford *et al.*, "The benefits of pesticides: a story worth telling," *Purdue University, Purdue Extension, West Lafayette, IN*, 2006.

[13] J. Jeyaratnam, "Acute pesticide poisoning: a major global health problem," *World Health Stat Q*, vol. 43, pp. 139-44, 1990.

[14] V. P. Androutsopoulos, A. F. Hernandez, J. Liesivuori, and A. M. Tsatsakis, "A mechanistic overview of health associated effects of low levels of organochlorine and organophosphorous pesticides," *Toxicology*, vol. 307, pp. 89-94, 2013.

[15] J. F. Shelton, I. Hertz-Picciotto, and I. N. Pessah, "Tipping the balance of autism risk: potential mechanisms linking pesticides and autism," *Environmental health perspectives*, vol. 120, p. 944, 2012.

[16] E. M. Roberts, *et al.*, "Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley," *Environmental health perspectives*, pp. 1482-1489, 2007.

[17] K. Lyall, R. J. Schmidt, and I. Hertz-Picciotto, "Maternal lifestyle and environmental risk factors for autism spectrum disorders," *International journal of epidemiology*, vol. 43, pp. 443-464, 2014.

 ISBN: 978-1-61208-502-9

[18] O. Zerbo, A.-M. Iosif, L. Delwiche, C. Walker, and I. Hertz-Picciotto, "Month of conception and risk of autism," *Epidemiology (Cambridge, Mass.)*, vol. 22, p. 469, 2011.

[19] T. B. Hayes, V. Khoury, A. Narayan, M. Nazir, A. Park, T. Brown, *et al.*, "Atrazine induces complete feminization and chemical castration in male African clawed frogs (Xenopus laevis)," *Proceedings of the National Academy of Sciences*, vol. 107, pp. 4612-4617, 2010.

[20] C. Rowe, *et al.*, "Residential proximity to organophosphate and carbamate pesticide use during pregnancy, poverty during childhood, and cognitive functioning in 10-year-old children," *Environmental Research*, vol. 150, pp. 128-137, 2016.

[21] G. D. Shapiro, *et al.*, "Exposure to organophosphorus and organochlorine pesticides, perfluoroalkyl substances, and polychlorinated biphenyls in pregnancy and the association with impaired glucose tolerance and gestational diabetes mellitus: The MIREC Study," *Environmental research*, vol. 147, pp. 71-81, 2016.

[22] S. Mostafalou and M. Abdollahi, "Pesticides and human chronic diseases: evidences, mechanisms, and perspectives," *Toxicology and applied pharmacology*, vol. 268, pp. 157-177, 2013.

[23] M. R. Bonner, *et al.*, "Occupational Exposure to Pesticides and the Incidence of Lung Cancer in the Agricultural Health Study," *Environ Health Perspect*, *pp. 1-31*, 2016.

[24] M. C. Alavanja, M. K. Ross, and M. R. Bonner, "Increased cancer burden among pesticide applicators and others due to pesticide exposure," *CA: A Cancer Journal for Clinicians*, vol. 63, pp. 120-142, 2013.

[25] L. C. Yee and Y. C. Wei, "Current modeling methods used in QSAR/QSPR," *Statistical Modelling of Molecular Descriptors in QSAR/QSPR, Volume 2*, pp. 1-31, 2012.

[26] C. O. X. Z.Wang, Quantitative Structure-Activity Relationship (QSAR) models", *University of Leeds*, 2013

[27] S. Lapenna, M. F. Gatnik, and A. P. Worth, *Review of QSA R Models and Software Tools for Predicting Acute and Chronic Systemic Toxicity*: Publications Office of the European Union Luxembourg, 2010.

[28] www.epa.gov., Proposed Approach to Efficiently Develop Physiologically Based Pharmacokinetic (PBPK) & Physiologically Based Pharmacokinetic-Pharmacodynamic (PBPK-PD) Models for Pesticides, [retrieved June 2016]

[29] J. B. Knaak, *et al.*, "Parameters for carbamate pesticide QSAR and PBPK/PD models for human risk assessment," in *Reviews of environmental contamination and toxicology*, ed: Springer, pp. 53-212, 2008

[30] A. J. Bednarska, P. Edwards, R. Sibly, and P. Thorbek, "A toxicokinetic model for thiamethoxam in rats: implications for higher-tier risk assessment," *Ecotoxicology*, vol. 22, pp. 548-557, 2013.

[31] S. E. Lacher, "P-Glycoprotein Transport in Pesticide Pharmacokinetics and Toxicity: Investigating a Link to Parkinson's Disease risk," 2013.

[32] S. C. Wason, T. J. Smith, M. J. Perry, and J. I. Levy, "Using physiologically-based pharmacokinetic models to incorporate chemical and non-chemical stressors into cumulative risk assessment: A case study of pesticide exposures," *International journal of environmental research and public health*, vol. 9, pp. 1971-1983, 2012.

[33] M. L. Rigas, M. S. Okino, and J. J. Quackenboss, "Use of a pharmacokinetic model to assess chlorpyrifos exposure and dose in children, based on urinary biomarker measurements," *Toxicological Sciences*, vol. 61, pp. 374-381, 2001.

[34] Z. Lin, *Integrating experimental and physiologically based pharmacokinetic modeling approaches to evaluate neurotoxicity of the herbicide atrazine across the lifespan*: uga, 2013.

[35] C. Lu, C. M. Holbrook, and L. M. Andres, "The implications of using a physiologically based pharmacokinetic (PBPK) model for pesticide risk assessment," *Environmental health perspectives*, pp. 125-130, 2010.

[36] M. Blomhøj, T. Kjeldsen, and J. Ottesen, "Compartment models," *Latest version available at: http://www4. ncsu. edu/~ msolufse/Compartmentmodels. pdf*, [retrieved December 2014]

[37] R. E. Baynes, K. J. Dix, and J. E. Riviere, "Distribution and Pharmacokinetics Models," *Pesticide Biotransformation and Disposition*, p. 117, 2012.

[38] T. Joseph Kumar Reddy, and K. Pallavi. *Compartment Modelling*. *Vignan Pharmacy College* , 2011

[39] B. Meibohm and H. Derendorf, "Pharmacokinetic/pharmacodynamic studies in drug product development," *Journal of pharmaceutical sciences*, vol. 91, pp. 18-31, 2002.

[40] J. R. Vallabhanen. "Pharmacokinetic models", *Malla Reddy College of Pharmacy, 2014*

[41] S. R. Crowell, *et al.*, "Preliminary physiologically based pharmacokinetic models for benzo [a] pyrene and dibenzo [def, p] chrysene in rodents," *Toxicology and applied pharmacology*, vol. 257, pp. 365-376, 2011.

[42] J. C. Lipscomb, S. Haddad, T. Poet, and K. Krishnan, "Physiologically-based pharmacokinetic (PBPK) models in toxicity testing and risk assessment," in *New Technologies for Toxicity Testing*, ed: Springer, 2012, pp. 76-95.

[43] P. T. S. Office of Prevention, U.S. Environmental Protection Agency, "Physiologically-Based Pharmacokinetic/Pharmacodynamic Modeling: Preliminary Evaluation and Case Study for the N-Methyl Carbamate Pesticides," 2003.

[44] S. F. Sundlof, J. E. Riviere, and A. L. Craigmill, *Handbook of comparative veterinary pharmacokinetics and residues of pesticides and environmental contaminants*: CRC Press, 1995.

[45] R. Krieger, "Chapter 46.3 Pharmacokinetc approaches applied to organophosphae insecticides," in *Handbook of Pesticide Toxicology, Two-Volume Set: Principles and Agents*. vol. 1, ed: Academic Press, 2001.

[46] E. Hodgson, *Pesticide biotransformation and disposition*: Academic Press, 2012.

[47] S. F. Sundlof, J. E. Riviere, and A. L. Craigmill, "Principle of interspecies extrapolation," in *Handbook of comparative veterinary pharmacokinetics and residues of pesticides and environmental contaminants* ed: CRC Press, 1995, pp. 29-30.

[48] J. G. Wagner, "Properties of the Michaelis-Menten equation and its integrated form which are useful in pharmacokinetics," *Journal of pharmacokinetics and biopharmaceutics*, vol. 1, pp. 103-121, 1973.

[49] R. Mehvar, "Principles of nonlinear pharmacokinetics," *American Journal of Pharmaceutical Education*, vol. 65, p. 178, 2001.

[50] M. Stroppolo, M. Falconi, A. Caccuri, and A. Desideri, "Superefficient enzymes," *Cellular and Molecular Life Sciences CMLS*, vol. 58, pp. 1451-1460, 2001.

[51] G. Picard, and C. Trottier, (2016). *MAT-265 Équations différentielles.*

 ISBN: 978-1-61208-502-9

[52] M. Douai. (2016). *13. Equations differentielles lineaires du second ordre a coeficients costants*.

[53] J. Griggs. (2016). *Second-Order Linear Differential Equations*.

[54] Z. S. Tseng. (2016). *Second Order Linear Differential Equations*.

[55] M. Arrou-Vignod, and J. Millaud, (2007). *Equations differerntielles lineaires a coefficients constants, cas des equations d'ordre 1 et 2*.

[56] M.-A. Warmerdam, "Department of Pesticide Regulation," 2008.

[57] R. E. Baynes and E. Hodgson, "Absorption and distribution of toxicants," *A Textbook of Modern Toxicology*, p. 77, 2004.

[58] W. Huisinga, W. Liebermeister, and T. Jahnke, "Pharmakokinetik: Mathematische Modelle und ihre Anwendung."

[59] J. Yu, "A subcellular compartmental modeling approach to pulmonary drug development," The University of Michigan, 2011.

[60] C. Timchalk, R. Nolan, A. Mendrala, D. Dittenber, K. Brzak, and J. Mattsson, "A physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) model for the organophosphate insecticide chlorpyrifos in rats and humans," *Toxicological Sciences*, vol. 66, pp. 34-53, 2002.

[61] D. K. Singh, *Pesticide Chemistry and Toxicology*: Bentham Science Publishers, 2012.

[62] F. Whitford, T. Fuhremann, K. Rao, G. Arce, J. E. Klauning, and A. Blessing, "Pesticide toxicology: evaluationg safety and risk," in *Pesticide toxicology: evaluationg safety and risk*, ed: Pardue University, 2003.

[63] F. M. Fishel, "Pesticide Toxicity Profile: Organophosphate Pesticides," *Gainesville: University of Florida Institute of Food and Agricultural Sciences*, 2005.

[64] F. M. F. O. Norman Nesheim, and Mark Mossler. (2013). *Toxicity of Pesticides*.

[65] U. E. P. Agency. (2016). *Assessing Human Health Risk from Pesticides*.

[66] U. S. G. Survey. (2016). *Sources of nutrients and pesticides*.

[67] L. Nasreddine and D. Parent-Massin, "Food contamination by metals and pesticides in the European Union. Should we worry?," *Toxicology letters*, vol. 127, pp. 29-41, 2002.

[68] J. F. W. C. A. Commission and W. H. Organization, "Guidelines for predicting dietary intake of pesticide residues," 1997.

[69] J.-C. Leblanc, L. Malmauret, T. GuÉrin, F. Bordet, B. Boursier, and P. Verger, "Estimation of the dietary intake of pesticide residues, lead, cadmium, arsenic and radionuclides in France," *Food Additives & Contaminants*, vol. 17, pp. 925-932, 2000.

[70] S. Humbert, M. Margni, R. Charles, O. M. T. Salazar, A. L. Quirós, and O. Jolliet, "Toxicity assessment of the main pesticides used in Costa Rica," *Agriculture, ecosystems & environment*, vol. 118, pp. 183-190, 2007.

 ISBN: 978-1-61208-502-9

TABLE I. PHARMACOKINETIC MODEL PARAMETERS

Studied Pesticide	**PK parameters extraction**						
	Parameters	***Parameter description***	***Value***	***Species***	***Administrated Dose***	***Mode of exposure***	***References***
Thiazol-2-14C, Oxadiazin-4-14C	ka (h^{-1})	Absorption rate constant (gut)	--	Rats	0.5 mg. kg-1 body weight	intravenous exposure	{Agnieszka Bednarska(1, 2), Peter Edwards(1), Richard Sibly(3), Pernille Thorbek}
	ke (h^{-1})	Elimination rate constant (urine)	0.4				
	ka (h^{-1})	Absorption rate constant (gut)	2.2		0.5 mg. kg-1 body weight	Bolus gavage exposure	
	ke (h^{-1})	Elimination rate constant (urine)	0.25				
	ka (h^{-1})	Absorption rate constant (gut)	1.03		100 mg kg-1 body weight		
	ke (h^{-1})	Elimination rate constant (urine)	0.25				
Paraquat	CLF (L/hr)	apparent Oral Clearance	0.473	FVB Wild-type and mdr1a(-/-)/1b(-/-) Mice	--	Single Paraquat Oral Dose	[31]
	Vdss (L)	apparent Volume of Distribution	1.77				
	ka (h^{-1})	Absorption rate constant (gut)	1.81				
Atrazine	ka_{1C} (h^{-1})	Gastric absorption rate constant	0.2	Adult male C57BL/6 mice	250, 125, 25, and 5 mg/kg body weight	oral gavage for 10 days	[34]
	k_{a2C} (h^{-1})	Gastric-emptying rate constant	0.7				
	ka_{3C} (h^{-1})	Intestinal absorption rate constant	0.018				
Organophosphate Parathion and Diazinon	$t_{1/2}$ (h)	Biological half life (single compartment model)	5.08	Rabbit	1.5 mg/kg of Body Weight	Intavenous	[45]
	Vdss (l/kg)	apparent Volume of Distribution	14.24				

 ISBN: 978-1-61208-502-9

Studied Pesticide	**PK parameters extraction**						
	Parameters	***Parameter description***	***Value***	***Species***	***Administrated Dose***	***Mode of exposure***	***References***
	CL(L/h/kg)	Clearance rate	3.59				
	$t_{1/2}$ (h)	Biological half-life (single compartment model)	0.021	Rabbit	3 mg/kg of Body Weight	Oral	
	Vdss (L/kg)	apparent Volume of Distribution	7.58				
	CL(L/h/kg)	Clearance rate	--				
	$t_{1/2}^{\alpha}$ (h)	Distribution half-life (two compartments model)	0.13				
	$t_{1/2}^{\beta}$ (h)	Removal half-life (two compartments model)	1.08				
	CL(L/h/kg)	Clearance rate	6.59	Piglet	2.8 mg/kg of Body Weight	Intravenous	
	Vdss (L/kg)	Apparent volume of distribution	2.6				
	CL(L/h/kg)	Clearance rate	4.42	Pig	1 mg/kg of Body Weight	Intravenous	
	Vdss (L/kg)	Apparent volume of distribution	9.76				
	CL(L/h/kg)	Clearance rate	4.60	Rat	80 mg/kg of Body Weight	Oral	
	Vdss (L/kg)	Apparent volume of distribution	22.95				
	$t_{1/2}$ (h)	Biological half-life (single compartment model)	2.55				
	CL(L/h/kg)	Clearance rate	4.69	Rat	5 – 10 mg/kg of Body Weight	Intravenous	
	Vdss (L/kg)	Apparent volume of distribution	20.01				
	$t_{1/2}^{\alpha}$ (h)	Distribution half-life (two compartments model)	0.33				
	$t_{1/2}^{\beta}$ (h)	Elimination half-life (two compartments	4.70				

 ISBN: 978-1-61208-502-9

Studied Pesticide	**PK parameters extraction**						
	Parameters	***Parameter description***	***Value***	***Species***	***Administrated Dose***	***Mode of exposure***	***References***
		model only)					
TCP	k_a (h^{-1})	Absorption half-life constant	1.5	Human Volunteers	0.5 mg/kg of Body Weight		
	$t_{1/2}^{absorption}$ (h)	Absorption half-life	0.5				
	k_e (h^{-1})	Elimination rate constant	0.0258				
	$t_{1/2}^{elimination}$ (h)	Elimination half-life	20.9				
	k_a (h^{-1})	Absorption rate constant	0.0308	Human Volunteers	5 mg/ kg of Body Weight		
	$t_{1/2}^{absorption}$ (h)	Absorption half-life	22.5				
	k_e (h^{-1})	Elimination rate constant	--				
	$t_{1/2}^{absorption}$ (h)	Elimination half-life	30				

 ISBN: 978-1-61208-502-9