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1 **Aggregating exposures & cumulating risk for Semivolatile Organic**

2 **Compounds: A review**

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13 **ABSTRACT**

14 Increasingly, health risk assessment is addressing multiple pathway exposures to multiple
15 contaminants. We reviewed aggregated exposure and cumulative risk approaches for
16 contemporary and ubiquitous semivolatile organic compounds (SVOC). We identified 22
17 studies aggregating exposure pathways, and 31 cumulating risk. Exposure aggregation is
18 based on the addition of pathway-specific doses, using kinetic modeling where it exists, and
19 classic external dose equations otherwise. In most cases, exposure is dominated by a single
20 route or source of exposure - mainly the oral pathway - via dietary or non-dietary exposure.
21 Preferential routes and sources of exposure are influenced by SVOC physical-chemical
22 properties such as vapor pressure. The cumulative risk approach for contaminants is based on
23 dose addition. Simple sum of hazard quotient (Hazard Index: HI) is the most commonly used
24 cumulative risk assessment approach, while Relative Potency Factor (RPF) appeared to be the
25 best suited – although this calls for a level of toxicological information that limits the number
26 of compounds that can be studied simultaneously. Where both were performed, moving from
27 HI to more refined approach produced similar results. In conclusion, both approaches -
28 exposure aggregation and cumulative risk - rely on simple assumptions. Nevertheless, they
29 allow uncertainty to be reduced, in comparison with source-by-source or chemical-by-
30 chemical approaches.

31 **KEY WORDS**

32 Mixture; contaminants; environmental exposure; health; exposure pathway; cumulative risk
33 assessment; chemical.

34

35 INTRODUCTION

36 People are continuously and increasingly exposed to a multitude of organic chemicals
37 (NHANES 2015) from various sources (e.g. food, dust, cosmetics and personal care products
38 (C&PCPs), textiles and materials) and media (e.g. air, water and soil), and by different routes
39 of exposure such as inhalation, ingestion or dermal contact. Organic chemicals include a high
40 number of compounds having various physical-chemical properties, and can be classified as
41 volatile, semivolatile or non-volatile compounds. Semivolatile organic compounds (SVOCs)
42 are defined as having a boiling point temperature of between 240 –and 400 °C (NF ISO
43 16000-6, 2006). This group includes a high number of organic molecules from different
44 chemical families (e.g. phthalates, bisphenols, polycyclic aromatic hydrocarbons (PAHs),
45 organophosphorus (OPs), organochlorines (OCs), synthetic musks, polychlorinated biphenyls
46 (PCBs), polybromodiphenylethers (PBDEs)). The scientific community’s growing interest in
47 studying exposure to SVOCs is motivated by a rise in their use in consumer products as well
48 as by improved analytical techniques that have shown their ubiquity, for example, in
49 dwellings (Rudel et al. 2003; Weschler and Nazaroff 2008). Moreover most are reprotoxic
50 (Peretz et al. 2014; Kay et al. 2014), neurotoxic (Muñoz-Quezada et al. 2013; Costa et al.
51 2014), or carcinogenic compounds (Armstrong et al. 2004; IARC 2015a, 2015b), and have
52 been found in human biological fluids (blood and urine).

53 When evaluating the impact of SVOC exposure on human health, exposures may be assessed
54 using either external or internal doses. External dose is estimated from contamination data and
55 human parameters such as body weight, inhalation and dust ingestion rate... Using a
56 pharmacokinetic model or absorption factors, it can be converted to internal dose. Internal
57 dose is preferentially assessed by biomonitoring. Biomonitoring data directly reflect internal
58 aggregate exposures and could, with back calculation using pharmacokinetics models, inform
59 as to the external dose attributable to each exposure pathway. However, using biomonitoring

60 data does not inform on the source of exposure that is so useful for prevention strategies.
61 Once exposure is assessed, the risk may be assessed by comparing exposures to a
62 toxicological reference value. This value may be expressed as an external dose for a unique
63 route of exposure, i.e. a reference dose or acceptable daily intake for ingestion (or a reference
64 concentration for inhalation). They are usually estimated from an indicator of the dose-
65 response relationship in laboratory mammals to which uncertainty factors are applied to take
66 into account inter/intra-species differences (Dybing et al. 2002). For some chemicals, internal
67 reference dose are proposed such as biomonitoring equivalent which are estimates of the
68 concentration of the substance (or a metabolite) in blood or urine that is consistent with the
69 reference dose (Hays and Aylward 2009).

70 In the case of indoor SVOCs, exposure occurs via different sources and media and concerns
71 many compounds simultaneously. Multiple exposure to mixtures is now widely recognized
72 and addressed, notably by international and national institutions in charge of risk assessment.
73 In the WHO/IPCS Framework for Risk Assessment of Combined Exposures to Multiple
74 Chemicals, aggregate exposure is defined as exposure to the same substance from multiple
75 sources, via multiple pathways, and routes (Meek et al. 2011). Cumulative risk assessment
76 linked to co-exposure to different substances is also recommended when feasible (Meek et al.
77 2011).

78 The objective of this study is to review the methods employed in the literature regarding (1)
79 exposure aggregation to an SVOC excluding biomonitoring and (2) cumulative risk
80 assessment for a mixture of SVOCs.

81 **METHODS**

82 The search covered the period from 1985 until 2016. Publications were selected in line with
83 the following criteria: addressing SVOC human exposure, aggregating at least two routes of
84 exposure for one SVOC or assessing cumulative risk to at least two SVOCs. Because they do
85 not provide methods for the aggregation of several routes of exposure; publications that
86 considered exposures to an SVOC from different sources (e.g. foodstuff) but via a single
87 exposure route (e.g. ingestion) were discarded, even though aggregation was the mentioned
88 terminology. Using the Web Of Knowledge™ website (Thomson Reuters,
89 www.webofknowledge.com), publications were selected primarily by searching in the field
90 “topic” (title, abstract and key words): ((exposure AND (assessment OR evaluation) AND
91 (cumulat* OR aggregat*) AND (chemicals OR products OR substances OR compounds OR
92 pollutants) AND health) OR (PBPK AND (SVOC OR pesticide OR phthalate OR flame
93 retardant OR plasticizer OR PCB OR musk OR PAH OR organochlor* OR organophosph*
94 OR pyrethroid) NOT (rat* OR mice OR mouse OR bear). Secondly, selected publications
95 were screened on the basis of the subject-title match. Thirdly, those publications remaining
96 were subjected to an exhaustive abstract reading in order to remove those which did not
97 address the research subject and to separate publications performing exposure aggregation
98 from those dealing with cumulative risk assessment (CRA). Publications identified in the
99 reference list of others were added. Since the objective was to review methods, publications’
100 results are presented only where they allow the comparison of different methods.

101 Regarding publications that aggregated exposure, the following items were retrieved:
102 references, chemical class, exposure characteristics (source, media, and route of exposure),
103 exposure modeling (type of approach: deterministic or probabilistic, type of aggregated dose,
104 and the doses aggregation level: external or internal), and whether comparison with
105 biomonitoring data was made. Regarding publications that cumulated risks, the following

106 items were retrieved: references, number of chemical cumulated, SVOC selection criteria
107 (related to occurrence and toxicity), CRA characteristics (grouping by chemical class or not,
108 the dose calculation basis, and the method employed), and toxicity indicators characteristics
109 (type, source, point of departure, and type of toxicological endpoint).

110 **RESULTS AND DISCUSSION**

111 This search identified 22 publications that carried out an exposure aggregation from at least
112 two routes of exposure to an SVOC and 31 publications that carried out a CRA to at least two
113 SVOCs.

114 1. Aggregate exposure assessment

115 Table 1: Publications performing exposure aggregation on semivolatile organic compounds.

116 [Table 1]

117 Twenty-two publications carrying out SVOC exposure aggregation were identified, and these
118 are presented in Table 1. This may seem few, given the high number of compounds
119 concerned, yet assessments are often focused on exposure to a compound from various
120 sources but via a single exposure route. The oldest dates back to 1998 and from 2010 to 2016,
121 one to five publications per year were retrieved from the literature.

122 Seven publications aggregated exposure to OPs, six to phthalates, four to pyrethroids, three to
123 PAHs, three to PBDEs, three to phenols, two to PCBs, two to parabens, one to musks, one to
124 OCs, one to polychlorinated naphthalenes (PCNs), one to perfluoroalkyl acids (PFAAs) and
125 one to replacement flame retardants (RFRs). Residential exposure was studied most (18
126 publications), addressing exposure to air (n=16), dust (n=13), surfaces (n=7), soil (n=6) and
127 dental sealing (n=1). Fourteen of the publications addressed dietary exposure: all were
128 interested in solid food exposure, four took drinking water into account and three were also
129 interested in breast milk exposure. Three publications addressed occupational source with
130 exposures to air (n=2) or to air and soil (n=1). Two publications addressed exposure to
131 C&PCPs.

132 Human exposure to these various sources and media could occur via three pathways:
133 inhalation, ingestion or dermal contact. Of the 22 publications selected, a majority (n=14)
134 aggregated exposure by three pathways, whereas the rest did so by two pathways. As an
135 example, Gosens et al. (2014) aggregated exposure to four parabens contained in C&PCPs by
136 dermal and ingestion pathways. The reason put forward for not studying exposure by
137 inhalation was that none of the investigated C&PCPs applied by spray contained parabens.
138 Another reason for not studying a route of exposure is negligible absorption, in comparison
139 with the other pathway. For instance, Wilson et al. (2003) assessed the aggregated exposure
140 by ingestion and inhalation of 37 SVOCs present in several media (indoor and outdoor air,
141 indoor dust, soil and food) rather than by dermal absorption because this was considered
142 negligible in comparison. Because of recent advances in dermal exposure importance
143 (Weschler and Nazaroff 2012) and modeling (Gong et al. 2014; Shi and Zhao 2014; Morrison
144 et al. 2016), this pathway is expected to be more systematically considered in the future.
145 Indeed human experiments with exposure to phthalates have proven this pathway to be
146 significant for some SVOCs (Weschler et al. 2015).

147 Aggregation of exposure was always conducted by estimating exposure for each route
148 individually, then summing them. These exposures were often assessed by employing classic
149 external dose equations (e.g. U.S. EPA, 1992) combining human parameters (such as weight,
150 body surface area, inhalation rate, amount of ingested dust and frequency of use) with media
151 or product contamination (e.g. SVOC concentration in the media or product). Thirteen
152 publications have used this method. An alternative could be the employment of
153 pharmacokinetic (PK) and/or pharmacodynamics (PD) models to aggregate exposure to
154 individual SVOCs by several routes, and provide an absorbed dose. The physiologically-
155 based pharmacokinetic model (PBPK), describes the physiological, biochemical, and
156 physical-chemical processes governing the absorption, distribution, metabolism, and excretion

157 of a xenobiotic in the body. It consists of a series of compartments receiving the xenobiotic
158 via systemic circulation. These models could also incorporate a pharmacodynamic dimension
159 (PBPK/PD) relating to processes leading to a critical health outcome (e.g. acetylcholinesterase
160 inhibition). PK and PD models require the same parameters as for external dose equations,
161 with the addition of physiological, physiochemical (e.g. partition coefficient) and biochemical
162 (e.g. metabolic rate constant) parameters. Eight publications have used PK models: four used
163 a PBPK model, two a one-compartment PK model and one a PBPK/PD model. The four
164 PBPK models were developed for three different chemical families (PAHs, pyrethroids and
165 OPs), the two one-compartment PK models for PBDE compounds and for PAH compounds,
166 whereas the PBPK/PD model was only developed for OP compounds – chlorpyrifos, to be
167 precise. When PK and/or PD models were available these appeared to be the preferred method
168 for assessment of overall exposure to an SVOC. However, because these are available only
169 for certain specific SVOCs, and because their construction entails high consumption of both
170 data and resources, they are not systematically used. In order to estimate and aggregate
171 exposures to an SVOC, some publications have also used specific exposure models, which
172 include PK modeling components, such as the Stochastic Human Exposure and Dose
173 Simulation model for multimedia (SHEDS-Multimedia) which was developed by the U.S.
174 EPA's Office of Research and Development to simulate aggregate exposure via dietary and
175 residential routes (inhalation and dermal contact) to a variety of environmental chemicals
176 such as pesticides, metals and persistent organic pollutants ([https://www.epa.gov/chemical-
177 research/stochastic-human-exposure-and-dose-simulation-sheds-estimate-human-exposure](https://www.epa.gov/chemical-research/stochastic-human-exposure-and-dose-simulation-sheds-estimate-human-exposure)).
178 Three publications used SHEDS-Multimedia to assess exposure to pyrethroid and OP
179 compounds. Another specific model is the Probabilistic Aggregate Consumer Exposure
180 Model (PACEM), first used by Gosens et al. (2014) to facilitate aggregate exposure
181 assessment of parabens compounds present in C&PCPs. However, though these are more

182 adaptable to various SVOCs than are PK and/or PD models, they could be limited by the use
183 of predefined scenarios (e.g. residential pesticide use scenarios using SHEDS-Multimedia,
184 such as indoor flying insect killer, pet treatment, vegetable patch, etc.) or data (e.g. Dutch
185 C&PCPs use data for PACEM). Compared to classical external dose modeling, most of the
186 time achieved with a deterministic approach, these models use distributions for the human
187 parameters inputs and contamination data in order to allow a probabilistic approach.

188 Exposure assessment to a contaminant could be expressed as an external or internal dose, the
189 latter reflecting contaminant uptake after crossing absorption barriers. Only Wilson et al.
190 (2003) and Roosens et al. (2010) expressed results as external doses for each route of
191 exposure. Fifteen other publications estimated internal doses for each route of exposure, and
192 five estimated internal dose only for the dermal pathway. Of these, nine publications used a
193 PK approach to convert external exposure into organ, tissue or fluid concentrations. Eleven
194 other publications converted external exposure into internal exposure by applying absorption
195 factors retrieved from the literature or considered a default value of 100%. For the dermal
196 pathway the authors used dermal absorption fraction (Shurdut et al. 1998; Duggan et al. 2003;
197 Linares et al. 2010; Gosens et al. 2014) or a transdermal permeability coefficient (Beko et al.
198 2013). Transdermal permeability coefficients are more precise, because they take into account
199 partition through the different layers of the skin to the dermal capillaries, and these were
200 recently available in the literature for several SVOCs (Weschler and Nazaroff 2012). This
201 explains why their use has increased since 2013 (in comparison with 1998) for dermal
202 absorption factors. Internal dose appears as the logical metric when considering aggregation
203 of exposure. The most sophisticated approach is PBPK modeling, followed by PK modeling,
204 use of absorption factor, or default 100% absorption. Using external doses (most often
205 observed for inhalation and ingestion) actually consists in considering that there is no

206 differential absorption between exposure routes. This should at least deserve an uncertainty
207 analysis with reported values for bioavailability.

208 Both external and internal exposure assessments require input parameters (such as human
209 parameters, media or product contamination data and specific parameters of SVOCs). With
210 regard to these parameters, single values could be used to conduct a deterministic approach. A
211 conservative choice of parameters is considered as a lower tier approach by several authors
212 (Delmaar and van Engelen 2006; Sarigiannis et al. 2013), and was indeed employed in ten
213 publications. A higher tier approach could be conducted by probabilistic analyses with Monte
214 Carlo simulation by introducing distributions rather than single values, and this was employed
215 by twelve authors. Both approaches were used and compared by Gosens et al. (2014) to
216 estimate aggregate exposure, by ingestion and dermal contact, to four parabens. Although
217 exposure assessment results were comparable in both approaches, internal exposures
218 estimated by the higher tier approach were always below those estimated by the lower tier
219 approach for each paraben. This result confirmed that a deterministic approach gave a good
220 conservative starting point for exposure assessment but that a probabilistic approach gave a
221 more realistic and more informative exposure assessment where enough data were available
222 (by, for example, allowing estimation of the proportion of population above the reference
223 dose, and enabling sensitivity analysis).

224 Most of the studies (n=16) aggregated exposures for an average individual using
225 representative data from a population, e.g. a specific age group. Six studies aggregated
226 exposures for specific individuals with their own data.

227 Most studies (n=16) compared their estimations of aggregate exposure to human
228 biomonitoring data (e.g. NHANES), and eleven of these found consistent results. A reason for

229 the discrepancies could be for instance the non-inclusion of a major pathway, such as diet for
230 phthalates (Beko et al. 2013).

231 It is noteworthy that the authors discussed the contribution made to exposure by each
232 pathway, source or media. The major route of exposure depends on: the studied compounds;
233 the conditions of exposure to these compounds (e.g. residential or occupational), the routes of
234 exposure assessed, and whether the population of interest included children more susceptible
235 to dust ingestion (Beamer et al. 2012; Wason et al. 2012; Gaspar et al. 2014; Mitro et al.
236 2016). Some authors investigated influent parameters such as SVOC physical-chemical
237 parameters with molecular weight (Beko et al. 2013), and vapor pressure (Wilson et al. 2003),
238 which are related to their partitioning among various media (e.g. indoor air, dust), leading to a
239 preferential route of exposure. As an example, Beko et al. (2013) found the dermal pathway to
240 be the major route of exposure for two phthalates (DnBP and DiBP). Xue et al. (2014) studied
241 exposure to seven pyrethroids when using, or not using, pesticide at home. These authors
242 found ingestion to be the major route of exposure in both cases, with dietary exposure being
243 the most contributive for the population not using pesticides, and non-dietary exposure for the
244 population that does use them. Zartarian et al. (2012) found the same results regarding
245 children's aggregate (dietary and non-dietary) residential exposure to permethrin. The
246 circumstance of exposure also has an influence. For example Wei et al. (2013) studied global
247 exposure to a pyrethroid during and after aircraft disinfection treatments, finding inhalation to
248 be the major route of exposure during the pre-flight spray, and dermal pathway to be the
249 major route of exposure for the residual treatment scenario. The dominant pathway may
250 change depending on exposure level. For example Trudel et al. (2011) found ingestion of food
251 to be the dominant pathway for several PBDEs up to about the 60th quantile of the total dose,
252 while oral and dermal uptake of dust dominated above the 60th quantile, because of a larger
253 variability of concentration and dust ingestion rate. Because few studies (n=6) addressed

254 global exposure to SVOCs via ingestion, inhalation and dermal contact to at least food, air,
255 dust or soil and objects (such as toys, clothing or indoor surfaces), it is difficult to determine a
256 general dominant pathway trend in global exposure assessment to SVOC. However, as
257 observed by Wilson et al. (2003), on the basis of 54 SVOCs, ingestion was found to be the
258 main route of exposure for the less volatile compounds, whereas inhalation was the most
259 significant for the more volatile compounds.

260 To summarize, choice of method depends strongly on research objectives. A PK and/or PD
261 model seemed preferential when assessing total exposure to an SVOC. However, because
262 they are available only for certain SVOCs, and because their construction involves high data
263 and resource consumption, a lower tier approach - such as employing external dose equation -
264 appeared to be more adequate (at least as a first step) and provided consistent estimations.
265 Inclusion of an uncertainty analysis in exposure assessment appears essential in this situation.

266 Lastly, even where exposure to an SVOC is governed by a major route, aggregating exposure
267 provides useful information regarding exposure characteristics such as influent media, or
268 variation between compounds of the same chemical family.. Aggregation of all routes of
269 exposure to an SVOC appears essential, especially when performing a risk assessment in a
270 second step.

271 2. Cumulative Risk Assessment

272 Table 2: Publications performing Cumulative Risk Assessment on semivolatile organic
273 compounds.

274 [Table 2]

275 Thirty-one publications conducting SVOC CRA were identified for inclusion in this review,
276 and these are presented in Table 2. The oldest dates back to 2003, and since 2009, from one to
277 seven publications per year were retrieved from the literature.

278 For each study, SVOCs were included in a CRA on the basis of their occurrence and/or a
279 similar pattern of toxicity. Firstly, regarding occurrence, dietary contamination was the most
280 used criterion (n=16), followed by the occurrence of SVOC metabolites in humans (n=8). In
281 addition, two studies chose on the basis of their presence in industrial emissions, three on their
282 presence in the residential environment, one on their presence in drinking water, one on their
283 presence in the water, sediment and biota of a specific river and lastly, four studies provided
284 no explanation regarding occurrence for the selection of compounds. Secondly, regarding
285 toxicity patterns for compound selection, having an anti-androgenic mechanism of action
286 (n=11), or inhibiting the acetylcholinesterase (AChE) mechanism (n=11) were the most
287 studied effects. In addition, sodium channel modulators, toxic effects on the nervous system,
288 toxic effects on the liver, the reduction of hepatic retinoid, and respiratory irritation were also
289 studied. Finally, five publications based their compound selection on multiple toxic effects.
290 Chemical classes investigated were: carbamates (CBs), OPs, OCs, PAHs, parabens, PBDEs,
291 PCBs, phenols, phthalates, polyfluoroalkylated substances (PFASs) and pyrethroids. In fact,
292 12 publications studied OP compounds, 11 phthalate compounds, 7 carbamate compounds
293 and 6 pyrethroid compounds. The scientific community's growing interest in OPs and
294 phthalates is driven by suspicion of toxic health effects, such as the anti-androgenic effects of
295 some phthalates on the male reproductive system (Joensen et al. 2012), or the neurotoxic
296 effects of some OPs (Mileson et al.1998), their ubiquitous occurrence in various media (Rudel
297 et al. 2003; Blanchard et al. 2014), and the acknowledged presence of these compounds and
298 their metabolites in human biological fluids (NHANES 2015), as well as - specifically for
299 OPs - the availability of relative potency factors (RPF) published by governmental agencies

300 (U.S. EPA 2006). Finally the review reveals that a majority of the publications (n=26)
301 performed CRA for SVOCs coming from the same chemical class and only five encompassed
302 compounds from different families.

303 A CRA can be performed using several methods that have been developed and used for
304 decades now, notably for regulatory purposes on polluted sites (U.S. EPA 1989). Most of
305 these are based on the following additivity assumptions, notably with the “Incremental
306 Lifetime Cancer Risk”, a sum of cancer risks commonly used in regulatory risk assessment.
307 “Dose additivity” assumes that each compound of a mixture is supposed to contribute to the
308 overall observed effect in proportion to its concentration (dose), with the assumption that
309 “toxicants in a mixture act upon similar biological systems and contribute to a common
310 response in proportion to their respective potencies” (Calabrese 1990). On the other hand,
311 “response additivity” assumes that each compound of a mixture is supposed to contribute to
312 the overall observed effect in proportion to its effect (response), with the assumption that
313 “toxicants in a mixture act upon dissimilar biological systems and act independently”
314 (Calabrese 1990). This notion does not take into account the possibility of such toxicological
315 interaction as antagonism or potentiation and could lead to biased estimation of the risk. For
316 example, Boon et al. (2008) have highlighted an overestimation when conducting a CRA to
317 OPs and carbamates exposures. Even though these are known for their common AChE
318 inhibiting activity, their specific mechanisms of action are different - indeed AChE receptor
319 binding is mostly irreversible regarding OPs whereas it is reversible regarding carbamates.
320 However, toxicological interaction (i.e. antagonism or potentiation) is mostly based on the
321 saturation phenomena of metabolic systems, which can be considered as never being achieved
322 regarding low, even sometimes very low (e.g. up to ng/m^3 in indoor air regarding several
323 SVOCs) (Blanchard et al. 2014) compound concentrations in the exposure media (ATSDR
324 2004). Nevertheless, an empirical analysis of low-dose synergy, by Boobis et al. (2011)

325 revealed results of low magnitude (1.5 to 3.5). Furthermore, the principal purpose of risk
326 assessments is to help regulatory or policy-making organizations make decisions and to
327 develop operative strategies regarding the control of human exposure to environmental,
328 residential and occupational pollutants, leading to consideration of the additivity assumptions
329 as operational.

330 Several CRA methods exist and the most commonly used in the literature are, from the lowest
331 to the highest tier, the Hazard Index (HI) method, the Point of Departure Index (PODI) and
332 the RPF approaches, described extensively elsewhere (U.S. EPA 2000; Sarigiannis and
333 Hansen 2012; Fournier et al. 2014a). Briefly, the HI method is based on the sum of hazard
334 quotients (HQ) for substances affecting the same target organ or system. For each substance
335 involved, the HQ is calculated by dividing exposure by reference dose (i.e. the level at which
336 no adverse effects are expected in humans) (U.S. EPA 2000). This method was used in 20
337 publications. Although it provides a transparent and comprehensive result (HI<1 indicates that
338 there is little likelihood that an adverse effect might be observed from chronic exposure) this
339 method is also a lower tier approach, because the reference doses are not necessarily
340 constructed with regard to the same target organ, and can sometimes be imprecise with regard
341 to the compounds' mechanism of action. However, it does allow the study of compounds
342 from different chemical classes, but affecting the same target organ or system. Four
343 publications are concerned in this review; all the others studied compounds from a single
344 class (n=16). In order to quantify interaction effects in a mixture, Ragas et al. (2011) followed
345 the interaction-based HI approach developed by the U.S. EPA (2000). This method assumes
346 that interactions among compounds in a complex mixture are dependent on those of all
347 possible binary combinations of the individual mixture components. The HI is multiplied by a
348 weight factor reflecting the significance of these interactions. The authors observed
349 interaction effects in two groups (with, for instance, four and two pesticides respectively) and

350 found that the interaction-based HI was always higher than the conventional one. However,
351 because of weak scientific evidence regarding the calculation procedure, and a weak empirical
352 basis regarding parameter values, the authors have warned that these interaction-based HIs
353 should be used with caution (Ragas et al. 2011).

354 The PODI approach differs from the HI in that the sum of exposures to each compound is
355 expressed as a fraction of its respective and comparable point of departure (POD) for effects
356 of toxicological relevance (for example, a benchmark dose) rather than a fraction of the
357 reference dose – inducing less uncertainty. The reciprocal of the PODI is the combined
358 margin of exposure (MOE) based on the sum of individual MOEs. For each compound
359 involved, the MOE is calculated by dividing its POD to human exposure (EFSA 2008). Three
360 of the publications used a combined MOE approach.

361 The RPF approach assumes similarity of mechanisms of action between individual
362 compounds and uses toxicity data for an index compound to normalize the potencies of each
363 other compound in a mixture. Usually the potencies are POD derived from dose-response
364 curves. The combined toxicity of the mixture corresponds to the sum of the potency
365 normalized doses to yield total equivalent exposure, expressed as index compound
366 equivalents, which is then compared to the reference dose of the index compound (EFSA
367 2008). This method was used in 13 publications. Seven publications studied compounds from
368 the same chemical class - mostly OPs (n=4) - whereas the others studied compounds from
369 different classes (n=6). Four of them applied a RPF approach class by class, whereas Caldas
370 et al. (2006) and Blaznik et al. (2015) performed a RPF approach to OP and CB compounds
371 having the same mechanism of action.

372 Several publications compared CRA methods. Three publications used both a RPF and a
373 combined MOE approach. One of these is interested in cumulating risks linked to exposure to

374 five PCBs, and although the authors found similar results with respect to estimates of median
375 MOE values, they pointed out that the advantage of the RPF approach is that it is more easily
376 implemented in practice, and accounts quantitatively for both variability and the various
377 uncertainties involved (Kalantari et al. 2013). Furthermore, RPF data published by the U.S.
378 EPA are available for the OPs (U.S. EPA 2006), CBs (U.S. EPA 2007), and pyrethroids (U.S.
379 EPA 2011). Benson et al. (2009) and Beamer et al. (2012) found similar results when using
380 both a RPF and an HI approach. Beamer et al. (2012) did not assess the potential added value
381 of a RPF approach to an HI approach, yet Benson et al. (2009) suggested using the less
382 complex HI approach for future CRA to simultaneous phthalates.

383 The reference doses employed by the authors could differ for a single SVOC according to: the
384 toxicological endpoint studied and the type of POD chosen (no observed adverse effect level
385 (NOAEL), lowest observed adverse effect level (LOAEL) or Benchmark Dose (BMD)); the
386 value of the uncertainty factor applied, and the date of construction, depending on the
387 organization producing these values (e.g. acceptable/tolerable daily intakes (A/TDI) from
388 EFSA or WHO, and reference doses (RfD) from U.S. EPA). Dewalque et al. (2014) and Gao
389 et al. (2016) both calculated HI to several phthalates using two different reference values, (1)
390 TDI from EFSA based on effects on reproduction and development and (2) reference dose
391 from Kortenkamp and Faust (2010) based on anti-androgenic effects. Each author found
392 different results, attesting to the fact that cumulative assessment is dependent on the reference
393 value taken into account.

394 Dose calculation for exposure estimation was based on contamination data alone in 21
395 publications and on both contamination and biomonitoring data in 9. Only Beko et al. (2013)
396 estimated daily intakes from both media phthalates compound contaminations (with the
397 exception of foodstuffs) and urinary concentrations of their metabolites before conducting a

398 CRA using an HI approach. The authors found an HI from urinary concentrations to be twice
399 as high as from media contaminations.

400 Following a tiered approach when conducting a CRA is now recognized by institutions such
401 as the EFSA's Scientific Panel on Plant Protection products and their Residues (PPR) which
402 recommends the use of tiered approaches when assessing risks of chronic exposure to
403 pesticide residues (EFSA 2008). Several authors of this review have confirmed the pertinence
404 of this recommendation for conducting a CRA on SVOC exposure. A lower tier method (such
405 as the HI approach) could be used as a first step, with recourse to a higher tier method (such
406 as the RPF approach) being justified where the outcome suggests further refinement is called
407 for.

408 CONCLUSIONS AND PERSPECTIVES

409 Aggregate exposures and cumulative risks need to be taken into consideration in addressing
410 total SVOC exposure and the overall risk they pose. In particular, the dermal pathway has
411 proven to be significant in the recent years. This literature review has revealed that relatively
412 simple approaches based on the sum of exposures, doses or effects can be useful, at least in a
413 first tier. However, these first-tier approaches carry their own uncertainties and should be
414 accompanied by an uncertainty analysis of simplifying assumptions. It is however important
415 to keep in mind that not choosing to aggregate exposures or cumulate risks creates more
416 uncertainty because of the implicit assumption of independence of exposures and effects.

417 This review has highlighted that, because they consider differential absorption rates related to
418 the different routes of exposure, as well as metabolism phenomena, pharmacokinetic models
419 are useful tools for aggregating exposure. Because these are currently available only for
420 certain SVOCs, there is a need for development of generic models for those SVOCs sharing
421 common toxicological effects (e.g. a PBPK model for reprotoxic SVOC). They could also be
422 used for reverse dosimetry using biomonitoring data.

423 When assessing cumulative risks to several compounds (e.g. in order to build a RPF), a
424 compromise needs to be reached between the exhaustiveness of the compounds list and the
425 required precision of the toxicity estimates for each substance involved in the mixture. A great
426 progress towards putting cumulative risk assessment into practice would be to generate
427 comparable toxicity data in order to build RPF. This may be achieved, for instance, with the
428 use of standardized high-throughput assays as developed last years by the US EPA (Kavlock
429 et al. 2012), associated with the development of omics strategies (i.e. proteomics or
430 transcriptomics). Recent works in these topics are very promising (Hannas et al. 2011;

431 Thomas et al. 2011, 2012; Van Ravenzwaay et al. 2014; Chauhan et al. 2016; Labib et al.
432 2016).

433 Both PBPK building and toxicity testing is time and resources consuming and a proposal
434 would be to focus efforts on ubiquitous compounds sharing, or suspected to share, the same
435 mechanism of action. A next step would be to identify compounds the populations are
436 frequently exposed to, and then define corresponding cumulative assessment groups, such it
437 has already be done for certain environments (Fournier et al. 2014b), or regulatory processes
438 (Boobis et al. 2008).

439

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Table 1: Publications including exposure aggregation on semivolatile organic compounds

References (year of publication)	Chemical class (nb. of publications)	Exposure pathways			Exposure modeling		Aggregation			Comparison with biomonitoring data
		Source	Media	Route	Source-to-external dose	External-to-internal dose	Approach	Type of aggregated dose	Aggregation level	
Ginsberg and Foos (2016)	Phthalates (1)	Dietary Residential	Food Breast milk Drinking water Indoor air Indoor dust Indoor objects Clothing	Dermal Ingestion Inhalation	External dose equation	Absorption factors	Deterministic	Internal	Average individual	Yes
Mitro et al. (2016)	Musks (1) Parabens (3) PFAAs (11) Phenols (7) Phthalates (8) RFRs (15)	Residential	Indoor air Indoor dust	Dermal Ingestion Inhalation	External dose equation	Dermal absorption factors	Deterministic	External (ingestion, inhalation) Internal (dermal)	Average individual	No
Gosens et al. (2014)	Parabens (4)	Personal care products	Personal care products	Dermal Ingestion	External dose equation and PACEM	Absorption factors	Deterministic Probabilistic	Internal	Individual	No
Gaspar et al. (2014)	Phthalates (2)	Residential	Indoor air Indoor dust	Dermal Ingestion Inhalation	External dose equation	Dermal absorption factors	Probabilistic	Internal	Average individual	No
Poet et al. (2014)	OPs (1)	Residential	Indoor air Indoor surface (carpet treated)	Dermal Inhalation	PBPK/PD model		Deterministic	Internal	Individual	Yes
Ortiz et al. (2014)	PAHs (1)	Occupational	Indoor air	Dermal Inhalation	PBPK model and simple one-compartment PK model		Deterministic	Internal	Individual	Yes
Xue et al. (2014)	Pyrethroids (7)	Dietary Residential	Food Indoor air	Dermal Ingestion Inhalation	SHEDS-Multimedia	PK model	Probabilistic	Internal	Average individual	Yes
Beko et al. (2013)	Phthalates (5)	Residential	Gas phase Particle phase Indoor dust	Dermal Ingestion Inhalation	External dose equation	Dermal absorption factor	Probabilistic	External (ingestion, inhalation) Internal (dermal)	Average individual	Yes
Wei et al. (2013)	Pyrethroids (1)	Occupational (aircraft disinfection)	Indoor air	Dermal Ingestion Inhalation	PBPK model		Probabilistic	Internal	Average individual	Yes
Wason et al. (2013)	Pyrethroids (3) OPs (2)	Residential	Indoor dust Indoor surfaces Soil	Dermal Ingestion	SHEDS-Multimedia		Probabilistic	Internal	Average individual	No

Beamer et al. (2012)	OPs (2)	Dietary Residential	Food Indoor air Indoor dust Indoor surfaces and toy	Dermal Ingestion Inhalation	PBPK model		Probabilistic	Internal	Individual	Yes
Zartarian et al. (2012)	Pyrethroids (1)	Dietary Residential	Food Indoor air	Dermal Ingestion Inhalation	SHEDS-Multimedia	PK model	Probabilistic	Internal	Average individual	Yes
Trudel et al. (2011)	PBDEs (8)	Dietary Residential	Food Indoor air Indoor dust Indoor surfaces Soil	Dermal Ingestion Inhalation	External dose equation	Absorption factors	Probabilistic	Internal	Average individual	Yes
Roosens et al. (2010)	PBDEs (6)	Dietary Residential	Food Breast milk Indoor air Indoor dust Soil	Ingestion Inhalation	External dose equation	No	Probabilistic	External	Average individual	No
Von Goetz et al. (2010)	Phenols (1)	Dietary Residential	Food Breast milk Indoor air Indoor dust Dental sealings	Ingestion Inhalation	External dose equation	Absorption factors	Deterministic	Internal	Average individual	Yes
Linares et al. (2010)	PAHs (16) PCBs (7) PCNs (5)	Dietary Occupational (petrochemistry)	Food Drinking water Air Soil	Dermal Ingestion Inhalation	External dose equation	Dermal absorption factor	Probabilistic	External (ingestion, inhalation) Internal (dermal)	Average individual	No
Lu et al. (2010)	OPs (1)	Dietary Residential	Food Drinking water Indoor air Indoor dust Toy surfaces Soil	Ingestion Inhalation	PBPK model		Deterministic	Internal	Individual	Yes
Lorber (2007)	PBDEs (9)	Dietary Residential	Food Indoor air Indoor dust Soil	Dermal Ingestion Inhalation	Simple one-compartment PK model		Deterministic	Internal	Average individual	Yes
Wormuth et al. (2006)	Phthalates (8)	Dietary Residential Personal care products	Food Indoor air Outdoor air Indoor dust Clothing Personal care products	Dermal Ingestion Inhalation	External dose equation	Absorption factors	Deterministic	Internal	Average individual	Yes
Duggan et al. (2003)	OPs (31)	Dietary Residential	Food Drinking water Non-dietary	Dermal Ingestion Inhalation	External dose equation	Dermal absorption factor	Deterministic	External (ingestion, inhalation) Internal (dermal)	Average individual	Yes
Wilson et al. (2003)	OCs (9)	Dietary	Food	Ingestion	External dose	No	Deterministic	External	Individual	Yes

	OPs (2) PAHs (20) PCBs (18) Phenols (3) Phthalates (2)	Residential	Indoor air Outdoor air Indoor dust Soil	Inhalation	equation					
Shurdut et al. (1998)	OPs (1)	Dietary Residential	Food Indoor air Indoor surfaces	Dermal Ingestion Inhalation	External dose equation	Dermal absorption factor	Probabilistic	External (ingestion, inhalation) Internal (dermal)	Average individual	Yes

OCs = Organochlorines; OPs = Organophosphorus; PACEM = Probabilistic aggregate consumer exposure model; PAHs = Polycyclic aromatic hydrocarbons; PBDEs = Polybrominated diphenyl ethers; PCBs = Polychlorinated biphenyls; PCNs = Polychlorinated naphthalenes; PFAAs = Perfluoroalkyl acids; RFRs = Replacement flame retardants; SHEDS-multimedia = Stochastic human exposure and dose simulation model for multimedia.

Table 2: Publications performing cumulative risk assessment (CRA) on semivolatile organic compounds

References (year of publication)	Number of chemicals cumulated	SVOCs selection criteria		CRA			Toxicity indicators			
		Occurrence	Toxicity	Grouping by chemical class	Dose calculation basis	Method	Type	Source	Type of toxicological endpoint	POD
Li et al. (2016)	Pyrethroids (7)	Dietary contamination	AChE inhibitors	Yes	Contamination data	HI	ADI RfD	na	na	na
Lozowicka et al. (2016)	CBs (1) OPs (3) Pyrethroids (3)	Dietary contamination	AChE inhibitors Sodium channel modulators	Yes	Contamination data	HI	ADI	EFSA	na	na
Quijano et al. (2016)	CBs (7) OPs (12) Pyrethroids (7)	Dietary contamination	AChE inhibitors	Yes	Contamination data	RPF	RPF ADI	U.S. EPA	AChE activity	NOAEL BMD
Zentai et al. (2016)	OPs (24)	Dietary contamination	AChE inhibitors	Yes	Contamination data	RPF	RPF RfD	Boon et al. (2008) Caldas et al. (2006) JMPR	AChE activity	NOAEL BMD ₁₀
Gao et al. (2016)	Phthalates (3)	Urinary measurement	Multiple Anti-androgenic	Yes	Biomonitoring data	HI	TDI RfD	EFSA Kortenkamp and Faust (2010)	Effects on reproduction and development Anti-Androgenic	NOAEL LOAEL BMD
Ogbeide et al. (2016)	OCs (13)	Water, sediment and biota contamination	-	Yes	Contamination data	HI	RfD	U.S. EPA	na	na
Jensen et al. (2015)	Different classes of pesticides (20)	Dietary contamination	Multiple	No	Contamination data	HI	ADI	EC EFSA JMPR	na	na
Blaznik et al. (2015)	CBs (4) OPs (10)	Dietary contamination	AChE inhibitors	No	Contamination data	RPF	RPF RfD	Boon et al. (2008) European commission	AChE activity	NOAEL LOAEL BMD ₁₀
Kranich et al. (2014)	Phthalates (5)	-	Anti-androgenic	Yes	Biomonitoring data	HI	TDI RfD	EFSA Kortenkamp and Faust (2010)	Effects on reproduction and development Anti-Androgenic	NOAEL LOAEL BMD
Peluso et al. (2014)	OCs (9)	Water contamination	Multiple	Yes	Contamination data	HI	RfD	U.S. EPA IRIS	na	na
Xue et al. (2014)	Pyrethroids (7)	Residential (consumer use) Urinary measurement	-	Yes	Contamination data	RPF	RPF RfD	U.S. EPA	na	na
Chang et al. (2014)	Phthalates (7)	-	Anti-androgenic	Yes	Contamination data	HI	TDI RfD	EFSA WHO U.S. EPA	Hepatotoxicity Anti-Androgenic	na

Dewalque et al. (2014)	Phthalates (4)	Urinary measurement	Anti-androgenic	Yes	Biomonitoring data	HI	TDI	EFSA	Effects on reproduction and development	NOAEL LOAEL BMD
							RfD	Kortenkamp and Faust (2010)	Anti-Androgenic	
Christensen et al. (2014)	Phthalates (5)	Dietary contamination Urinary measurement	Anti-androgenic	Yes	Biomonitoring data	HI	TDI	EFSA	Effects on reproduction and development	NOAEL LOAEL
							RfD	Denmark EPA	Anti-Androgenic	
Jardim et al. (2014)	OPs (7) Pyrethroids (4)	Dietary contamination	Multiple	Yes	Contamination data	RPF	RPF	Caldas et al. (2006) U.S. EPA	AChE activity	NOAEL BMD
							RfD	JMPR U.S. EPA		
Leeman et al. (2013)	CBs (7) OPs (26) Phthalates (6)	Dietary contamination	AChE inhibitors AChE inhibitors Anti-androgenic	Yes	Contamination data	RPF	RPF	Calculated	na	na
							ADIRfD	EU Pesticide Database		
Borg et al. (2013)	PFASs (17)	Dietary contamination Urinary measurement	Multiple	Yes	Biomonitoring data	HI	RfD	Calculated	Hepatotoxicity Reproductive toxicity	NOAEL LOAEL BMD
Beko et al. (2013)	Phthalates (3)	Residential (dust contamination) Urinary measurement	Anti-androgenic	Yes	Biomonitoring data Contamination data	HI	TDI	EFSA	Effects on reproduction and development	NOAEL LOAEL
Kalantari et al. (2013)	PCBs (5)	Dietary contamination	Reduction of hepatic retinoid	Yes	Contamination data	RPF Combined MOE	RPF	Kalantari et al. (2012)	Hepatic retinoids	na
							RfD	Calculated	Body/liver weights	BMD ₀₅
Beamer et al. (2012)	OPs (2)	Dietary contamination Residential (media contamination)	AChE inhibitors	Yes	Contamination data	RPF HI	RPF RfD	U.S. EPA	ChE inhibition (plasma, RBC) ChE inhibition (brain)	BMD ₁₀ NOAEL
Søeborg et al. (2012)	Phthalates (4)	Urinary measurement	Anti-androgenic	Yes	Biomonitoring data	HI	TDI	EFSA	Effects on reproduction and development	NOAEL LOAEL
							RfD	Kortenkamp and Faust (2010)	Anti-Androgenic	
Ragas et al. (2011)	CBs (1) Neonicotinoids (1) OCs (1) OPs (2) Pyrethroids (1)	Dietary contamination	Nervous system Liver	Yes	Contamination data	HI	ADI	EC WHO	na	na
Koch et al. (2011)	Phthalates (3)	Urinary measurement	Anti-androgenic	Yes	Biomonitoring data	HI	TDI	EFSA	Effects on reproduction and development	NOAEL LOAEL
Kortenkamp and Faust (2010)	OCs (1) OPs (1) Parabens (2) Phenols (1)	-	Anti-androgenic	No	Contamination data	HI	RfD	Calculated	Anti-androgenic	NOAEL LOAEL BMDL

	Phthalates (5) PBDEs (1) Other classes of pesticides (4)						ADI	EFSA		
Linares et al. (2010)	PAHs (3)	Chemical and petrochemical industries emissions	-	Yes	Contamination data	HI	RfD	U.S. EPA	na	na
Bosgra et al. (2009)	OPs (31)	Dietary contamination	AChE inhibitors	Yes	Contamination data	RPF Combined MOE	RPF	Calculated	AChE activity	BMD ₂₀
Benson (2009)	Phthalates (5)	-	Anti-androgenic	Yes	Biomonitoring data	RPF HI	RfD	Calculated	Anti-Androgenic	NOAEL LOAEL BMDL
Boon et al. (2008)	OPs (26) CBs (8)	Dietary contamination	AChE inhibitors	Yes	Contamination data	RPF	RPF	Calculated	AChE activity	NOAEL BMD ₁₀
							RfD	JMPR		
Durmusoglu et al. (2007)	Phenols (1) PAHs (4)	Tire industries emissions	Respiratory irritation	No	Contamination data	HI	RfD	U.S. EPA	Not specific	na
Caldas et al. (2006)	OPs (22) CBs (3)	Dietary contamination	AChE inhibitors	No	Contamination data	RPF	RPF	Calculated	AChE activity	NOAEL BMD ₁₀
							RfD	JMPR		
Castorina et al. (2003)	OPs (11)	OPs commonly applied that metabolize dialkyl compounds	AChE inhibitors	Yes	Biomonitoring data	RPF Combined MOE	RPF	Calculated	AChE activity	BMD ₁₀

AChE = acetylcholinesterase; ADI = Acceptable daily intake; CBs = Carbamates; DNEL = Derived no effect level; EC = European Commission; HI = Hazard index; HQ = Hazard quotient; JMPR = Joint FAO/WHO Meeting on Pesticide Residues; MOE = margin of exposure; na = not available; OCs = Organochlorines; OPs = Organophosphorus; PAHs = Polycyclic aromatic hydrocarbons; PCBs = Polychlorinated biphenyls; PFAs = Perfluoroalkoxy alkanes; POD = Point of departure; POPs = Persistent organic pollutants; RBC = Red blood cell; RfD = Reference dose.