Analysis of chemical contaminants

Critical analysis of an article and review of related literature

Article:

"Solid phase extraction of carbamate pesticides with porous organic polymer as adsorbent followed by high performance liquid chromatography-diode array detection"

(Paper 20)

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Abstract of the report:

Carbamates insecticides are first described with regard to their properties, biological activity, toxicology and regulation. The determination method reported in the article of Wang et al. (2019) is then described and illustrated in a flow diagram. The method validation is assessed considering the guidelines given in the course. The assessment confirms that the validation was imperfect yet acceptable. Finally, a brief commented overview of alternative methods for sample preparation, separation and detection of carbamates is provided, along with a personal viewpoint.

Contaminants overview:

The five n-methylcarbamates insecticide active substances considered in the article of Wang et al. (2019) are **metolcarb (**(3-methylphenyl) N-methylcarbamate), **carbaryl** (naphthalen-1-yl N-methylcarbamate), **isoprocarb** ((2-propan-2-ylphenyl) N-methylcarbamate), **bassa** ((2-butan-2-ylphenyl) N-methylcarbamate) and **diethofencarb** (propan-2-yl N-(3,4-diethoxyphenyl)carbamate). "Bassa" is a trade name for **fenobucarb**. This last designation will be used in this report. See annexes for representation and IUPAC names of the analytes.

- **Description**: carbamates are compounds derived from carbamic acid (R1,R2,R3 = H) (Fig. 1). The five compounds are also aromatics. They are soluble in polar organic solvents (> 700 g/kg in cyclohexane and 100 g/L in xylene) and exhibit very low solubility in water and apolar solvents [1].

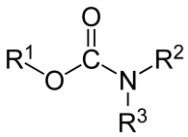


Figure 1

Carbamates-based insecticides are thus essentially formulated as dusts, wettable powders, liquid concentrates, granules, or baits [1,2].

- **Biological activity & toxicity**: Carbamate insecticides inhibit irreversibly and competitively acetylcholinesterase (AChE), an enzyme responsible for the breakdown of the neurotransmitter acetylcholine in synapses [3,4,5]. Organophosphates pesticides (OP) also target AChE but irreversibly and non-competitively [5], so toxicity symptoms on mammals are very similar for both classes [6]. Carbamates are thus regarded as safer than OP because acute toxicity is temporary and more easily treated [5,6]. Carbamates used as insecticides are selected for their lower affinity for mammalian AChE [5]. Carbaryl is highly toxic for aquatic wildlife and is directly toxic to pollinators [2]. Ecotoxicity is not well defined for the other compounds, but similar effects may be expected. Oral LD_{50} (rat) ranges from 230 (carbaryl) to >5 mg/kg (diethofencarb) and skin LD_{50} (rat) ranges from 896 (metolcarb) to >5 mg/kg (fenobucarb, diethofencarb). Table 1 displays acute toxicity data. No other adverse effects are reported except

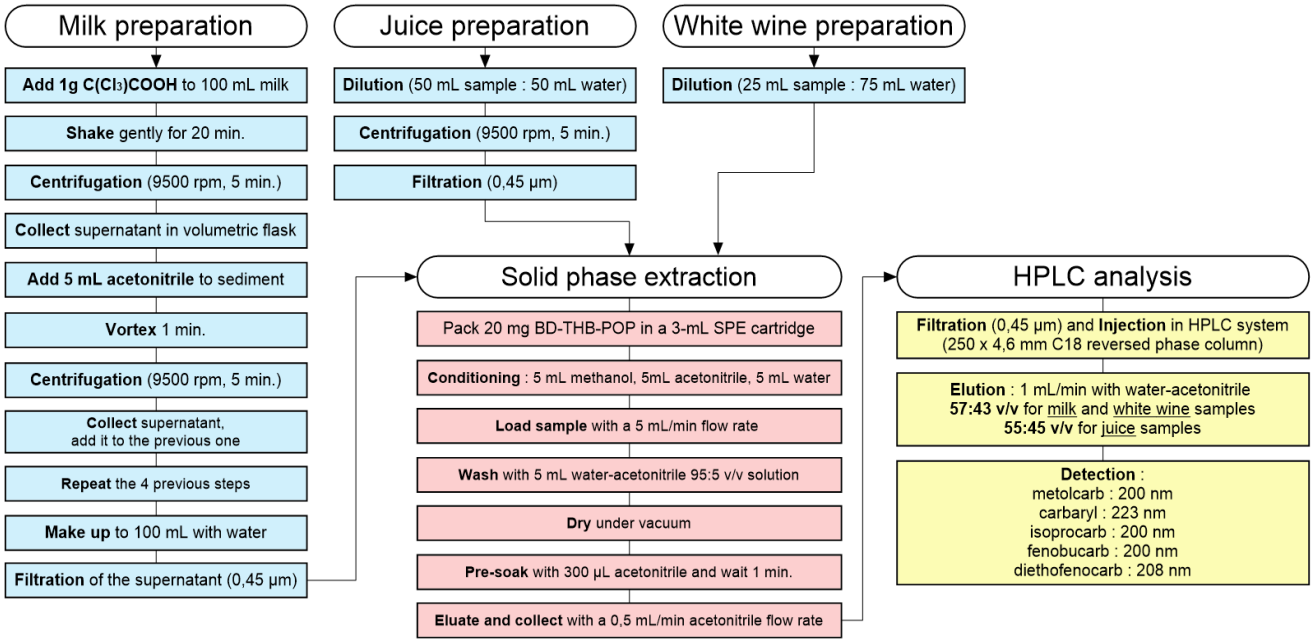
for carbaryl which is likely carcinogenic, mutagenic and has endocrine disruptor effects at lower doses [7].

- **Regulation**: Only diethofencarb is approved in EU. Standard EU MRL of 0,01 mg/kg apply for the five carbamates, except diethofencarb which is allowed to 0,8 mg/kg in pear and 0,9 mg/kg in wine. Table 2 reports regulation for the five studied carbamate pesticides in EU and the US.

Matrices:

The method was developed for carbamates determination in milk, white wine and (fruit) juice. Carbamates are used as insecticides against insects in vineyards and orchards, which explains their potential presence in fruits and wine; as well as against ticks, fleas, lices and other blood-sucking pests on cattle, which explains their possible presence in milk [1].

Method reported in the article :



Sample preparation method: **White wine** is expected to be clear of particles and only requires a four-fold dilution before SPE. **Juice** may contain micro-pulps and requires centrifugation and filtration (0,45 µm) of the supernatant after a two-fold dilution and before SPE. **Milk** is a more complicated matrix (fat globules, casein micelles...). First, carbamates and caseins of a 100 mL sample are precipitated with 1g trichloroacetic acid. After gentle shaking for 20 minutes and centrifugation at 9500 rpm for 5 minutes, the supernatant is collected in a volumetric flask. Then, 5 mL of acetonitrile are added to the sediments in order to solubilize carbamates before vortexing for 1 minute, centrifugation as previously, collecting supernatant

and adding it to the previous one. Again, 5 mL of acetonitrile are added and the subsequent steps performed. The volume of the previously collected supernatant aliquots is made up to 100 mL and filtered (0,45 µm) before SPE.

Solid phase extraction (SPE): 20 mg of benzidine trihydroxybenzene porous organic polymers (BD-THB-POP) are packed in a 3-mL cartridge. Conditioning is achieved with 5 mL methanol, then 5 mL acetonitrile, then 5 mL water. The sample is loaded with a flow rate of 5 mL/minute. The column is then washed with 5 mL of a water-acetonitrile (95:5 v/v) solution and dried under vacuum afterwards. The column is pre-soaked with 300 µL acetonitrile for 1 minute prior to elution with acetonitrile with a 0,5 mL/minute flow rate. (Elution time is not mentioned and depends on the analytes' affinity for the BD-THB-POP solid phase).

Instrumental method: the eluate is filtered (0,45 µm) and injected in the HPLC system (250 x 4,6 mm C18 reversed phase column). Isocratic elution is achieved with a flow rate of 1 mL/minute of water acetonitrile solution (57:43 v/v for milk and white wine samples and 55:45 v/v for juice samples). Detection is achieved with a diode array detector (DAD) at 200, 223, 200, 200 and 208 nm for metolcarb, carbaryl, isoprocarb, fenobucarb and diethofencarb respectively.

Validation assessment:

"Good validation practices" are preceded by a check mark (✓) while "Mistakes or abuses" are preceded by a cross mark (✗).

- **Repeatability**: Five parallel analyses of matrices spiked with each of the carbamates at 2,0 - 12,0 -60,0 µg/L (for milk and white wine samples) and 1,0 - 6,0 - 30,0 µg/L (for juice samples) were performed.
  - ✗ Only on five replicates; EU standards recommend at least 6 replicates [9] ;
  - ✗ Regarding EU standards, repeatability should be assessed at "concentrations equivalent to 1, 1,5 and 2 times the minimum required performance limit or 0,5, 1 and 1,5 times the permitted limit." [9], that is to say 5,0 - 10,0 and 15,0 µg/kg (lowest MRL = 10 µg/kg).
  - ✗ Variability of the method and instrumentation alone are not distinguished.
- **Reproducibility** : Not assessed.
- **Recovery (Trueness) and accuracy** : same analysis as repeatability.
  - ✓ Recoveries are given for each compound and matrix using matrix matched calibration
  - ✓ with an associated RSD.

✗ Recoveries were calculated only on 5 replicates (at least 6 required).

✗ Trueness was not assessed compared to reference materials or other methods

- **Linear range** :
  - Calibration type : **matrix matched** : pesticide-free matrices were spiked with the analyte.

  ✓ Takes into account (immediate) matrix effect.

  - Concentrations : White wine and milk : 1,0 - 2,0 - 4,0 - 8,0 - 20,0 - 40,0 - 80,0 - 120,0 - 320,0 µg/L ; Juice : 0,5 - 1,0 - 2,0 - 4,0 - 10,0 - 20,0 - 40,0 - 80,0 - 160,0 µg/L)

  ✓ More than six points are included in the calibration curve with good repartition (close to a geometrical serie) with more points near the origin.

  ✗ The residuals (instead of "r") should be indicator of linearity as and homoscedasticity.
- **Sensitivity** :

  ✓ LODs and LOQs are clearly expressed for each matrix and each analyte ;

  ✗ No RSD associated with LOD and LOQ measurement, unknown repetitions ;

  ✗ The signal-to-noise ratio for LOQ determination is not specified ;
- **Specificity** : not assessed

  ✗ No assessment of specificity was performed. Potential deviations are not known.

Alternative methods for carbamates determination:

Alternative methods' performances for carbamates analysis are compared in Table 3.

- **Sample preparation :**
  - **Liquid phase (micro)extraction (LP(M)E)**: the official EPA method 632 for carbamates determination involves liquid-liquid (1L sample) with methylene chloride.

    - Single drop microextraction (SDME) [23]: good enrichment factor (86x).

    - Dispersive liquid-liquid microextraction (DLLME) [9]: This category includes many sub-categories (supercritical fluid, ionic liquids, ultrasound...). Ionic liquids were investigated along with GC for carbamates analysis [21] with satisfactory results.

    - Hollow-fiber liquid-phase microextraction (HF-LPME) [10,11,12]: a hollow-fiber (HF) with a porous membrane is soaked in the sample (donor phase) and filled with a non-miscible solvent (acceptor phase). Analyte partition occurs between the two phases in contact through the micro-pores. Their dimension prevents each solvent from flowing to the other side of the membrane. Extraction can be enhanced by pumping "fresh" solvent through a "U"shaped fiber 10] or with electrophoretic mobility (charged analytes) by inserting electrodes inside and outside of the HF [11]. Three-phase systems also exists: donor and acceptor phase are miscible,

but the membrane is imbibed with a non-miscible third solvent (preventing inter-solubility) [11].

Three articles with two-phases HF were included in this review: toluène in polypropylene fiber [13], octadecyl-graphene in octanol in polypropylene fiber [14] and octanol in carbon nanotube fiber [15].

- **Solid liquid extraction** :

- Solid phase extraction (SPE) and microextraction (SPME) : consumes less solvents and have higher enrichment factors than LPE, and reusable often [16,17]. Graphene is often used

- Magnetic dispersive (micro)solid phase extraction (MSPE): Graphene-Fe nanoparticles were also investigated with attained enrichment factor from 364 to 434 [18]. Either with SP(M)E and MSPE, graphene [19] is extensively investigated in literature for its capacity to adsorb carbamates.

- **Separation and detection methods :**

- Gas chromatography with FID, MS or NPD detectors [20,21]: hydrolysis and derivatization are required prior to analysis because of heat-sensitivity time-consumming. PTV inlet is a more expensive alternative. Even if GC performances are good, LC is preferred as it is more compatible with multi-residue analysis (MRM) and LC-MS/MS do not require derivatization.

- High performance liquid chromatography with DAD or MS/MS detectors [16,17,18]: a C18 reversed phase is the more common for carbamates analysis. UPLC-MS/MS exhibited the highest throughput (total run time: 8 min.) and sensitivity similar to GC, with the ability to detect heat-sensitive carbamates intact. Sample preparation remains the limiting step. HPLC-DAD is the most popular method as this instrumentation is very common and performances and cost are well balanced.

- Electrochemical biosensors (amperomerometry) [22]: they are cost- and time-efficient (instrumentation is limited to an amperometer, no sample preparation, reusable probes) but also tedious to prepare and not specific at all (all carbamates and OP are equally detected because sensing is based on AChE inhibition). This method has a great potential for screening purpose.

- Micellar electrokinetic chromatography (MEKC) [23,24]: this technique is a kind of capillary electrophoresis in which charged surfactants are added to allow separation of

uncharged analytes. Detection is achieved either with DAD (allowing distinction between carbamates) or amperometric detection (no distinction allowed between carbamates). MEKC hardly attain HPLC performances and, more importantly, instrumented / automated MEKC is not as common as HPLC.

Personnal considerations:

- Despite the number of "mistakes" observed in the method validation, the validation performed by Wang et al. (2019) seems reliable. The "defaults" observed are very common in the literature, thus Wang et al. (2019) are doing as well as commonly accepted validations.

- In this study in particular, even if residuals are not assessed for normality and linearity, r values are so high (0,9956 to 0,9998) that linearity may reasonably assumed.

- Variability should be explained simultaneously as RSD and SD in order to make comparison easier. In the example hereunder, by only examining mean value and RSD, it is not easy to understand which variable has the lowest absolute variability.

Mean value	Standard deviation	Relative standard deviation
5,7	0,5	8,77 %
8,2	0,6	7,3 %

- A more complete validation assessment could be carried with regards to other standards such as AOAC, ISO 5725, IUPAC or EURACHEM guidelines.
- A putatively efficient method for large scale carbamates analysis in food would be :
    1. Screening with electrochemical biosensor [25] as it is very fast (no sample preparation), inexpensive, reusable and regenerated within 80 min. The samples with a total carbamate + organophosphate content below the MRL of 0,01 mg/kg are negative. Samples exceeding that limit undergo the second step.

    2. Further analysis with HPLC-DAD or, even better, UHPLC-MS/MS for quantification of carbamates (and organophosphates) individually is performed on a limited number of samples thanks to the electrochemical biosensor screening.

- Beware that all the considerations in this report only take into account determination of carbamates only (**single residue method or SRM**). Multi-residue methods were not considered in the literature review although they are very common convenient Hence, a complete assessment should consider performances of multi-residue methods compatible with carbamates analysis.

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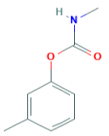
Annexes :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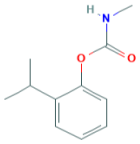
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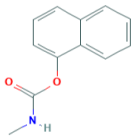
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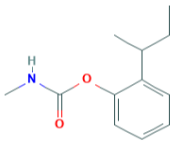
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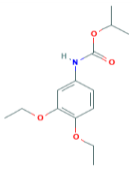
diethofencarb

Source : Pubchem[1]

Table 1 :
Median lethal doses of the 5 carbamates pesticides studied in rats (oral and skin application).

Active substance	LD_{50} (rat, oral)	LD_{50} (rat, skin)	Reference
metolcarb	268 mg/kg	896 mg/kg	Farm Chemicals Handbook., -(C212), 1991
carbaryl	230 mg/kg	4 g/kg	NIOSH, 2011 : USEPA, 2006
isoprocarb	450 mg/kg	>500 mg/kg	Farm Chemicals Handbook., -(C206), 1991 ; Pesticide Manual., 9(504), 1991
fenobucarb	350 mg/kg	>5 g/kg	Nippon Noyaku Gakkaishi. Journal of the Pesticide Science Society of Japan., 8(41), 1983 ; Pesticide Manual., 9(371), 1991
diethofencarb	>5 g/kg	>5 g/kg	Farm Chemicals Handbook., -(C106), 1991

National Center for Biotechnology Information. PubChem Database.

Table 2 :
Legal status and maximum residue levels of the 5 carbamates pesticides studied in EU and USA.

Active substance	Status		Maximum Residue Level (MRL)
	EU	USA	
metolcarb	not approved	not tolerated	EU : Default MRL of 0.01 mg/kg (Art 18(1)(b) Reg 396 / 2005)
carbaryl	not approved	tolerated	EU : from 0,01 mg/kg to 0,5 mg/kg (Part A of Annex I to Reg. 396/2005) USEPA : from 0,2 mg/kg in sweet potato to 22 mg/kg in spinach
isoprocarb	not approved	not tolerated	EU : Default MRL of 0.01 mg/kg (Art 18(1)(b) Reg 396 / 2005)
fenobucarb	not approved	not tolerated	EU : Default MRL of 0.01 mg/kg (Art 18(1)(b) Reg 396 / 2005)
diethofencarb	approved	not tolerated	EU : 0,01 mg/kg for all commodities except white wine (0,9 mg/kg) and pear (0,8 mg/kg).

[1] https://pubchem.ncbi.nlm.nih.gov/

Table 3 : Performance comparison of several methods for carbamates determination in various samples						
Separation / Detection	**Source**	**Sample preparation (matrix)**	**Linear range**	**LOD (S/N=3)**	**Recovery ± RSD (%)**	**Repeatability (Precision) (RSD in %)**
HPLC DAD	Wang et al., 2019 (studied article)	BD-THB-POP SPE (juice, white wine, milk)	1,0/2,0 - 320,0 ng/mL (milk and white wine) 1,0/0,5 - 160 ng/mL (juice)	from 0,06 (CRB, juice) to 0,4 ng/mL	82,0 - 110,0 ± 2,1 - 6,5	4,5 - 6,3 (n=5)
	Li et al., 2015	graphene/Fe MSPE (tomatoes) x 364 - 434 enrich.	5 - 200 ng/g (MTC) 10-200 ng/g (IPC) LOQ = 1,73 - 6,89 ng/g	0,58 - 2,06 ng/g	90,3 - 102,0 ± 1,21-5,93	intraday (n=?) : 0,69 - 6,51 interday (n=?) : 1,46 - 6,71
	Lin et al., 2010	DLLME (vegetables)	10,0 - 300 ng/g (CRB) 20,0 - 600 ng/g (IPC)	0,5 ng/g (CRB) 2,8 - 3 ng/g (IPC)	77,8 - 96,5 ± 2,7 - 6,3	2,9 - 3,3 (CRB) 3,4 - 4,7 (IPC) (n=5)
	Ma et al, 2015	HF-LLME propylene fiber + octadecyl - graphene in octanol (fruit)	0,5 - 100,0 ng/g (CRB) 1,0 - 100,0 ng/g (MTC, IPC, DFC)	0,6 (MTC) ; 0,2 (CRB) ; 0,6 (IPC) ; 0,4 ng/g (DFC)	90,3 - 107,4 ± 6,0 - 7,9	< 7,8
	Yang et al., 2007	HF-LLME propylene fiber + toluene (water)	10 - 100 ng/mL	1 ng/g (CRB) 5 ng/g (IPC) 3 ng/g (DFC)	82,0 - 102,0	2,0 - 6,2
	Zhao et al., 2011	HF-LLME carbon nanotube + octanol (fruit)	5 - 300 ng/g 1 - 300 ng/g	0,2 ng/g (CRB) 1,5 ng/g (MTC, DFC)	77,5 - 102,5 ± 3,1 - 7,2	3,1 - 7,7 (n=5)
UHPLC MS/MS	Shi et al., 2014	graphene SPE (water) x 34,2 – 51,7 enrich.	0,010 - 200 ng/mL (CRB) 0,025 - 100 ng/mL (IPC) 0,025 - 50 ng/mL (DFC) LOQ : 1,5 - 23,3 ng/mL	1,0 ng/L (CRB) 3,0 ng/L (IPC) 5,0 ng/mL (DFC)	81,2 - 107,9 ± not mentioned	5,54 (n=5, same cartridge) 1,27 - 8,13 (n = 7, between cartridges)
MEKC (ampero-metry)	Santalad et al., 2010	alkaline degradation - offline SPE (river water)	1 - 100 µM (IPC, CRB)	0,1 µM	< 9,5 (n=3)	interday : < 8,1
MEKC DAD	Moreno-González et al., 2011	DLLME sweeping concentration	4 - 200 ng/mL (CRB)	1 ng/mL (CRB)	93,4 - 101,7 ± 4,4 - 5,4	intraday : 0,69 - 6,51 interday : 1,46 - 6,71 (n=15)
GC-FID	Wu et al., 2016	poly(3,4-ethylenedioxythiophene) - ionic liquid DI-SPME (fruit & vegetables)	0,05 – 250 ng/mL	15,2 - 27,2 ng/L	87,5 - 106,5	< 6,1 on the same fiber (n = 5) 8,2 between fibers
GC-MS	Saraji et al., 2008	SDME (x86 enrich.) (water)	0,1 - 20 ng/mL(CRB) (cool on column inj.) 0,01 - 1 ng/mL (CRB) (deriv. + splitless inj.)	80 ng/L (cool on col. inj.) 3 ng/L (deriv. + splitless)	not mentioned	8,3 (cool on column inj.) 3,2 (deriv. + splitless inj.) (n=5)
Electro-chemical biosensors[2]	Song et al., 2016	none (fruits)	from 0,003 - 2,00 µM to 0,5 - 200 µM depending on the electrode	1,0 - 1400 nM according to the electrode	not retrieved	5.32 on the same sensor (n = 5)

GC : gas chromatography - HPLC-DAD : high performance liquid chromatography with diode array detector - MEKC : micellar electrokinetic chromatography (capillary electrophoresis) - DI-SPME : direct immersion solid phase microextraction - SDME : single-drop microextraction - MSPE : magnetic solid phase extraction - MTC : metcolcarb (165,19 g/mol) - CRB - carbaryl (201,22 g/mol) - IPC : isoprocarb (193,24 g/mol) - FBC : fenobucarb (207,27 g/mol) - DFC : diethofencarb (267,32 g/mol)

[2] (AuNPs)/(3-mercaptopropyl)-trimethoxysilane (MPS)/gold electrode (Au)