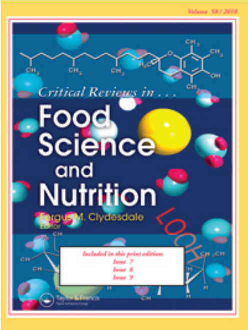

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Histamine food poisonings: A systematic review and meta-analysis

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ABSTRACT

Objective: The aim of this study was to assess the mean of histamine concentration in food poisoning.

Design: Systematic review and meta-analysis of reports published between 1959 and 2013.

Study selection: Main criteria for inclusion of studies were: all report types that present outbreaks of "histamine poisoning' or "scombroid syndrome" from food, including histamine content and type of food. Health status of people involved must be nonpathological.

Results: Fifty-five (55) reports were included, these studies reported 103 incidents. All pooled analyses were based on random effect model; histamine mean concentration in poisoning samples was 1107.21 mg/kg with confidence interval for the meta-mean of 422.62–2900.78 mg/kg; heterogeneity index (I2) was 100% ($P < 0.0001$); prediction interval was 24.12–50822.78 mg/kg. Fish involved in histamine poisoning was mainly tuna or Istiophoridae species. No clues of association between concomitant conditions (female sex, alcohol consumption, previous medication, and consumption of histamine releasing food) and histamine poisoning, were highlighted.

Conclusions: This is the first systematic review and meta-analysis that analyzes all the available data on histamine poisoning outbreaks evaluating the histamine concentration in food involved. Histamine mean concentration in poisoning samples was fairly high. Our study suffers from some limitations, which are intrinsic of the studies included, for instance the lack of a complete anamnesis of each poisoning episode.

Protocol registration: Methods were specified in advance and have been published as a protocol in PROSPERO database (18/07/2012 -CRD42012002566).

KEYWORDS
Scombroid syndrome; scombrotoxin fish poisoning; foodborne illness; outbreak; histamine intoxication

Introduction

Scombroid syndrome/histamine poisoning occurs worldwide and it is considered one of—if not—the most common form of toxicity caused by fish consumption (Dalgaard, Emborg, et al., 2008). The number of cases is increasing, in spite of the improved knowledge on seafood safety; this is due to a change in the way in which seafood, and mainly tuna, is eaten, that is, as steaks or hamburger (Becker, Southwick, et al., 2001), or as canned tuna recipes (sandwiches, salads, pizza) (Cattaneo, Stella, 2001; Mclauchlin, Little, et al., 2006). Less is known about foods other than seafood and it is of utmost importance to assess the impact of all food types on this syndrome to implement specific prevention measures.

Periodically reviews on this item have been published (Lehane, Olley, 2000; Hungerford, 2010), although containing a lot of data they are not systematic reviews. Systematic review has not yet been performed on histamine poisoning. To assess histamine level of food associated with histamine poisonings, in the light of objective criteria, could lead to reliable information useful to control this hazard.

The general aim of this review is to perform the first systematic review about histamine food poisoning and meta-analysis of histamine content in food involved in these outbreaks.

Methods

According to the Cochrane Collaboration (www.cochrane.org) guidelines, the methods of the analysis and inclusion criteria were specified in advance and documented in a protocol that has been published in the International prospective register of systematic reviews (PROSPERO WEB site: http://www.crd.york.ac.uk/PROSPERO), on 18/07/2012 with registration number CRD42012002566.

Criteria for considering studies for this review

Types of studies

All report types of histamine food poisoning from food were considered for inclusion in the review. Reports of histamine poisonings from non-food sources (such as experimental studies with histamine administration) were not considered for inclusion. Only reports with histamine concentrations determined by chemical and ELISA methods were included. If the report was an experimental comparative one (e.g., experimental group versus control group) only data of group where occurred foodborne histamine intoxication were considered.

Eligible studies included any histamine poisoning outbreaks or single episodes that reported a measure of the histamine

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content and the type of the food involved in histamine poisoning.

The spatial interval for considering studies was set as world-wide. The time interval was set from 1959 through 2013, because in 1959 there was the first application of a specific and accurate quantitative method, the fluorimetric assay of histamine in tissues (Shore, Burkhalter, et al., 1959). Reports (abstract and full text) written in English, Italian, French, German, Portuguese, and Spanish were considered; considering a full text in other languages was decided case-by case by the potential relevance for this review of its English abstract.

Population

Only clinically healthy subjects were included; food allergic patients and other very sensitive people (due to serious illness or anomalous physical or psychic conditions), preschooler (< 6 years old) and very old (> 80 years old) people were excluded. If in a study nothing was reported about health status of people involved in histamine poisoning the health status was recorded as "unknown."

Types of outcome measures

Primary outcomes

Number of histamine poisoning samples and histamine concentration in poisoning sample.

Secondary outcomes

Concomitant conditions relevant to histamine poisoning were considered as listed in Maintz and Novak (2007): female sex, previous medication, food description (fish species, food recipe), consumption of alcohol during the meal; consumption of food recipe with suggested histamine-releasing capacities.

Search methods for identification of studies

Search strategies were optimized to detect all reports of histamine poisonings from foods that met inclusion criteria. A main form of search strategy was designed and modified to meet settings of databases consulted. We systematically identified all potentially relevant reports through the main electronic databases (Table A); additional search was conducted by analyzing references of the selected articles.

Characteristics of consulted databases, specific search strategy and number of reports obtained, searched database are shown in Table A-1. Unpublished and ongoing studies were also considered and detected if existing. The main search strategy is presented in Fig. 1, search terms included the following key word: "histamine," "scombroid syndrome," "histamine poisoning," "food," "seafood," "meat products," "fish", "cheese", "beer", "wine", and "biogenic amines." To improve the effectiveness of keywords in the search strategy, a preliminary thesaurus study was performed. When multiple reports for a single study were present, it was used the most complete and updated version.

The literature search was conducted by two investigators (EC, FC) by aid of an information expert and by consulting with CB and PC. Two authors (CB and FC) independently selected potentially eligible studies for inclusion. The decision to include articles was made on the basis of the study title, then of the study abstract and finally of the full text; disagreements between reviewers were resolved by consensus; if no agreement was reached, a third author (PC) decided.

A data extraction sheet was developed and pilot-tested on a randomly-selected subgroup of included studies, data sheet was refined accordingly. One author (CB) extracted data from extraction sheet; data extracted were checked by a second author (FC). Disagreements were resolved by discussion between the two review authors; if no agreement was reached, a third author decided (PC).

A unique identifier of report was included in the characteristics recorded.

All quantitative measures of histamine content and measures of their variability; method of analysis used to determine food histamine content (if no method was mentioned the value was set to "unknown"); foods involved in histamine poisoning; primary and secondary outcome values; country or other identifier of geographic locations; people health category, i.e., if participants belonged to an excluded category and which was this category (if participants did not belong to above categories the status of "normal" was recorded); the presence of "heterogeneous food" (referring to more food types being associated with a single histamine mean value); other report characteristics useful to improve the quality of information.

Assessment of risk of bias in individual studies

Two reviewers (FC and CB) assessed the quality independently and any disagreements were resolved by discussion between the two review authors; if no agreement was reached, a third author decided (PC). Quality of included studies was considered a surrogate of risk of bias, so a quality score, of reports included in review based on additional relevant details other than inclusion criteria, was calculated. For each of the following seven items, a score of 1 was given if a value was present, 0 for absent value. The scores were then summed to give the final quality score (Murphy, Pfeiffer, et al., 2009). Variability estimate of histamine concentration, source of medical diagnosis (e.g., hospital m.d., family m.d.) or reasons given to present data as "histamine poisoning /scombroid syndrome," age, sex, health status, source of food involved in poisoning (restaurant, supermarket…), declaration of histamine content measurement method, number of patients involved in histamine poisoning; otherwise any element that could arise suspect of bias was recorded.

Summary measures

Concomitant conditions ("risk factors") relevant to histamine poisoning" outcome were summarized as a contingency table of the declared risk factors versus the number of their occurrences. The "number of histamine poisonings" outcome was summarized as the overall sum of histamine poisoning samples.

The summary measure of histamine concentration in sample was set to "log- mean"; this term is defined as the value of the estimate of the mean of the logarithms of the raw data. If this log-mean value was not be given in reports it was calculated with documented methods to yield a log-mean and its standard error (Quan, Zhang, 2003; Higgins, White, et al., 2008).

Excerpt from the systematic review protocol

"The search strategies will be focused to detect all reports of histamine poisonings from foods that meet inclusion criteria, so will be optimized accordingly to this purpose. A main form of search strategy will be designed and could be modified to meet settings of databases consulted. The strategy adopted and database on which was performed will be recorded. Main key-words will be: "histamine", "scombroid syndrome", "histamine poisoning", food, seafood, "meat products", fish, cheese, beer, wine, "biogenic amines". To improve the effectiveness of key-words in the search strategy a preliminary thesaurus study will be performed.

Replicate reports of the same data will be detected and only one report will be considered for inclusion in this review; reasons for the choice will be given and recorded. "

Main form of search strategy

Foreword

- if not specified, the mentioned keywords are meant to be searched both as "free search" keywords and "topic search" keywords:
- Key-words are "case-sensitive" written (lower case and upper case must be maintained when performing search)
- Logical operators and symbols are written in **bold** character

Legend

Suffix **.to** means: keyword will be searched only as "topic search" keyword
Suffix **.fr** means: keyword will be searched only as "free search"
<Keywords inside round brackets> means: phrase search
x/x (i.e. letter, slash, letter) means: degenerate letter, an appropriate "jolly character" has to be assigned to it.

Search Id	Key-words syntax	Notes
#1	**"**biogenic amines**".to**	-
#2	**"**scombroid syndrome**"**	-
#3	**"**histamine poisoning**"**	-
#4	#1 **or** #2 **or** #3	-
#5	"food poisoning"	-
#6	#4 **and** #5	
#7	food	-
#8	fish	-
#9	#7 **or** #8	-
#10	#6 **and** #9	-

Figure 1. Basic search strategy for identification of eligible studies.

Unit of the analysis

The unit of the analysis was the "histamine poisoning sample." This unit is defined as one "histamine poisoning" that occurred to one group of people (for "group" is meant one or more people) that ate one sample of food (for "sample of food" is meant one or more foods that were involved in one poisoning.

Histamine poisoning sample concept

One "histamine poisoning sample" (as defined above) led to one observation for each of the three outcomes considered; the observation formats were: a count of one (1) case in "assessment of valid histamine poisoning cases outcome," one histamine concentration log- mean in "histamine content" outcome and one list of values (i.e., the names of relevant concomitant factors) in "relevant concomitant factors" outcome. The number of patients involved in histamine poisoning sample was recorded. It was decided that all unexpected situations related to unit of analysis were assessed and managed and the management method recorded.

Methods to deal with missing data

Missing variability data in poisoning samples (when a mean is given for more than one food specimens being involved in a single poisoning sample) was derived with documented statistical method that were recorded.

If a single poisoning sample (unit of analysis) was associated with more than one food type ("heterogeneous food category") and histamine values of single foods were given but not the mean, it was planned that histamine content value had to be recorded as the log- mean of the values and variability estimate had to be calculated, the single values being recorded. If any of single values were missing, it was planned that the mean and variability estimated had to be calculated and the presence of missing values recorded.

Again, it was planned that if all, but one, values were missing histamine content had to be considered as a single value, this situation being recorded; moreover, all unexpected situations related to missing data had to be assessed and managed, possibly with documented methods that had to be recorded.

Synthesis of results methods

Punctual estimates and their 95% confidence intervals were calculated across all selected studies on statistical units according to the methods described above. Calculations were performed using the "metagen" procedure of "meta" package of R software (Schwarzer, 2010). As this meta-analysis was expected to yield a high degree of variability, the random effect model, described by DerSimonian and Laird (1986), was selected over the fixed effect model, because it incorporates within and between study variability. The chosen level of significance for statistical tests was $P < 0.05$. Heterogeneity, i.e., variability among records, was assessed by the I-squared (I^2) statistic (Higgins et al., 2003). Ninety-five percent (95%) prediction intervals were calculated by means of "metafor" R package (Viechtbauer, 2010).

Assessment of risk of bias across the studies

In general, due to the nature of this systematic review, no selective reporting bias was assessed; it was planned that, if there were clues of selective reporting, authors of reports had to be contacted asking them about other results or outcomes not reported and that, if this issue was not resolved, to decide, with reasons, to exclude such reports. Decision had to be kept independently by CB and FC; if disagreement occurred PC had to keep final decision. Whatever the decision, the bias clues detected had to be recorded.

About management of reporting biases, being this concept difficult to apply due to the nature of this review, it was decided to discuss the publication bias issue according to data scenarios encountered during the review development.

Additional analyses

Subgroup analysis about country or other identifier of geographic locations of histamine poisoning samples.

Subgroup analysis about groups: (1) fresh seafood, (2) frozen seafood, (3) canned seafood, (4) fermented seafood, (5) seafood other than 1,2,3,4; (6) cheese and dairy; (7) other foods.

Sensitivity analysis conducted by quality score or quality categories of the reports

Sensitivity analysis on histamine concentration outcome conducting meta-analysis separately on two groups: one containing reports where variability was not derived (variability data value given in report) and one where variability was derived (variability data value not given in report, variability data inferred from other data).

Results

Study selection

Searches yielded a total of 9390 references, after review and excluding duplicate reports 708 references were identified as potentially relevant. Of these, 556 records were included on the basis of title and abstract. We excluded 256 reports because they did not meet the adopted criteria and the full text of 300 reports was evaluated for report eligibility.

After excluding 248 full-text reports (corresponding to 285 poisoning samples), 52 reports (corresponding to 103 poisoning samples), listed in Table 1, were included in overall quantitative synthesis for outcomes "number of poisoning samples" and "concomitant conditions." Fourteen reports among them, corresponding to 15 poisoning samples, were selected for quantitative synthesis of outcome "histamine concentration in poisoning samples." The selection process is summarized in Fig. 2.

Characteristics of included studies

Below are summarized the characteristics of the 52 articles included; details are shown in Table 1. The overall analysis comprised a total number of 1171 people involved in 103

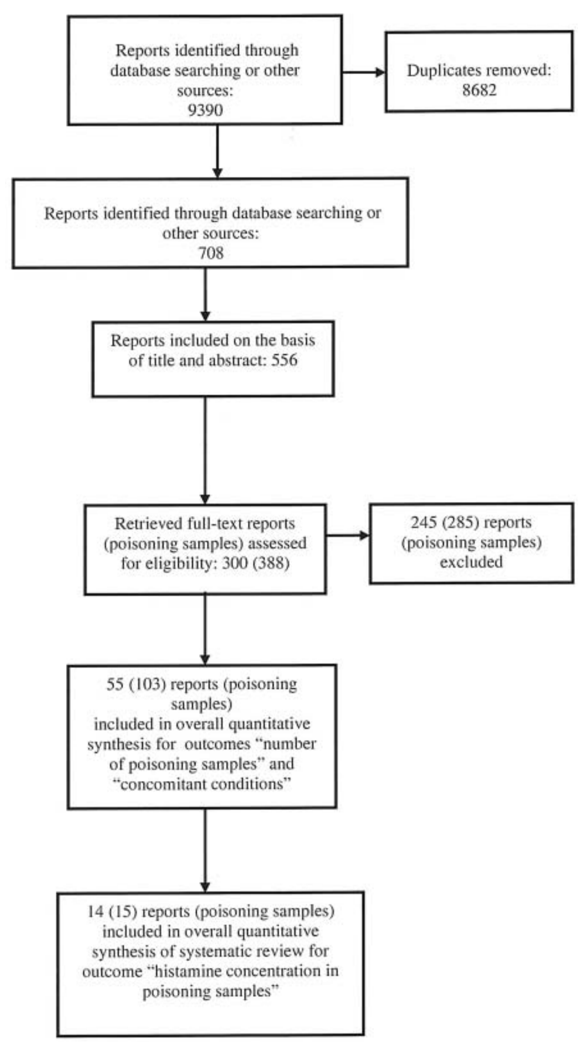

Figure 2. Flow chart of selection of reports for systematic review.

Table 1. Characteristics of studies included in meta-analysis. *N* for number of people involved in histamine outbreak, MD for missing data. Type of food (food category): (1) fresh, (2) frozen, (3) canned, (4) fermented, (5) other seafood, (6) cheese, and (7) other foods. Values of sample mean or sample standard deviation that were calculated have been rounded to two decimals.

Poisoning sample id / Reference	*N*	Location	Alcohol consumption	Previous medication	Female sex	Health status	Heterogeneous food	Histamine-releasing capacities food	Source of food	Type of food (food category)	Sample size	Sample mean (mg/kg)	Sample standard deviation (mg/kg)
Becker_2001_ET_aai_1[2]	11	North Carolina	MD	MD	MD	unknown	no	yes	restaurant	frozen tuna burgers (2)	2	2995	353.55
Becker_2001_ET_aai_3[2]	2	North Carolina	MD	MD	MD	MD	yes	yes	restaurant	tuna pieces in salad (5)	3	231.83	182.11
Bedry_2000_EN_mi1_1[12]	9	Bordeaux, France	MD	MD	no	unknown	no	yes	MD	cooked tuna (5)	MD	MD	MD
Bremer_2003_ET_cca_1[13]	5	Greater Auckland region (New Zealand)	MD	MD	MD	unknown	MD	yes	MD	Hot smoked kahawai (*Arripis trutta*) (5)	2	190-985	MD
Bremer_2003_ET_cca_2[13]	2	Greater Auckland region (New Zealand)	MD	MD	MD	unknown	MD	yes	MD	Hot smoked kahawai (*Arripis trutta*) (5)	2	1700-2100	MD
Bremer_2003_ET_cca_3[13]	16	Greater Auckland region (New Zealand)	MD	MD	MD	unknown	MD	yes	MD	Hot smoked kahawai (*Arripis trutta*) (5)	9	200-3940	MD
Chen_2008_ET_hhh_1[14]	7	Chiayi Prefecture, southern Taiwan	MD	MD	MD	unknown	yes	yes	MD	tuna damplings (5)	3	1608	59
Chen_2010_CB_zxc_1[15]	347	Kaohsiung City (Taiwan)	MD	MD	MD	unknown	no	yes	school canteen	fried fish cubes (*Tetrapturus angustirostris)* (5)	7	8114.4	19.94
Chen_2010_ET_fff_1[16]	7	Kaohsiung City (Taiwan)	MD	MD	MD	unknown	no	yes	restaurant	marlin fillets (5)	2	456.5	30.41
Chen_2011_ET_eee_1[17]	53	Kaohsiung City (Taiwan)	MD	MD	MD	unknown	no	yes	restaurant	mahi mahi fillets (5)	2	245	186.68
Chianèa_1998_ET_nnn_1[18]	MD	West Africa	MD	MD	MD	unknown	no	yes	seller on Africa coast	smoked swordfish (5)	9	2030-4750	MD
D'Aloia_2011_EN_5jb_1[19]	1	Brescia (Italy)	MD	MD	yes	healthy	no	yes	MD	grilled tuna (5)	1	>1000000	MD
Demoncheaux_ 2012_EN_99w_1[20]	71	Dakar, Senegal	MD	MD	no	mainly healthy	no	yes	military catering facility	yellowfin tuna (1)	2	4900	145
Doeglas_1967_ET_vvv_1[21]	1	Rotterdam	MD	MD	no	unknown	no	no	MD	brand of very old Gouda cheese (6)	1	850	MD
Eckstein_1999_EN_8f6_1[22]	30	Los Angeles	MD	MD	MD	unknown	no	yes	catering	escolar (*Lepidocybium flavobrunneum*) (2)	5	111-7670	MD
Emborg_2005_CB_kju_1[23]	8	Denmark	MD	MD	MD	unknown	no	yes	canteen	chilli-marinated steaks of Yellowfin tuna (5)	2	8100	1414.21
Emborg_2006_CB_kjs_1[24]	2	Denmark	MD	MD	MD	unknown	no	yes	home	Cold-Smoked Tuna (5)	2	4548	123
Emborg_2006_CB_kjs_2[24]	1	Denmark	MD	MD	MD	unknown	no	yes	private party	Cold-Smoked Tuna (5)	2	1972	4
Emborg_2006_CB_kjs_3[24]	10	Denmark	MD	MD	MD	unknown	no	yes	buffet at a canteen	Cold-Smoked Tuna (5)	2	914	8

(*Continued on next page*)

Table 1. (*Continued*)

Poisoning sample id / Reference	*N*	Location	Alcohol consumption	Previous medication	Female sex	Health status	Heterogeneous food	Histamine-releasing capacities food	Source of food	Type of food (food category)	Sample size	Sample mean (mg/kg)	Sample standard deviation (mg/kg)
Feldman_2005_EN_555_1[25]	42	Marin County, California, USA	MD	MD	no	unknown	no	yes	retreat centre	grilled escolar fish (*Lepidocybium flavobrunneum)* (2)	4	2825	741.06
Fernandez_2001_CB_3jd_3[26]	3	Valdecilla (Spain)	MD	MD	no	unknown	no	yes	home	*Scomberidae* (1)	1	5250	MD
Foo_1975_CB_h67_1[27]		Napler(New Zealand)	MD	MD	MD	unknown	no	yes	MD	kingfish (5)	1	7580	MD
Foo_1975_CB_jso_1[28]		Wellington(New Zealand)	MD	MD	MD	unknown	no	yes	MD	kahawai (5)	1	8000	MD
Foo_1977_CB_8sk_1[29]		Petone (New Zealand)	MD	MD	MD	unknown	no	yes	MD	canned skipjack (3)	12	567.08	388.08
Gellert_1992_82c_1[30]	8	Santa Ana, California	MD	MD	MD	unknown	no	yes	fish caught by a recreational fisher	smoked yellowfin and skijack tuna (5)	6	6960	MD
Guly_2006_EN79j _1[31]	5	Plymouth, UK	MD	MD	MD	unknown	no	yes	hotel buffet	fresh tuna (1)	1	>350	MD
Hall_2003_CB_h8s_1[32]	6	Canberra	MD	no	no	unknown; hypertension	no	yes	restaurant	yellowfin tuna (5)	2	480	14.14
Hobbs_1982_FC_55z_14[33]	4	UK	MD	MD	MD	unknown	no	yes	MD	Canned Tuna (3)	MD	1050	MD
Hobbs_1982_FC_55z_15[33]	2	Malaysia	MD	MD	MD	unknown	no	yes	MD	Canned Tuna (3)	MD	2900	MD
Hobbs_1982_FC_55z_16[33]	2	UK	MD	MD	MD	unknown	no	yes	MD	Canned Tuna (3)	MD	28	MD
Hobbs_1982_FC_55z_18[33]	1	UK	MD	MD	MD	unknown	no	yes	MD	Canned Tuna (3)	MD	35	MD
Hobbs_1982_FC_55z_20[33]	2	UK	MD	MD	MD	unknown	no	yes	MD	Canned Sardines (3)	MD	720	MD
Hobbs_1982_FC_55z_21[33]	1	UK	MD	MD	MD	unknown	no	yes	MD	Canned Anchovies (3)	MD	680	MD
Hobbs_1982_FC_55z_22[33]	3	UK	MD	MD	MD	unknown	no	yes	MD	Canned Sardines (3)	MD	3000	MD
Hobbs_1982_FC_55z_23[33]	1	UK	MD	MD	MD	unknown	no	yes	MD	Canned Tuna (3)	MD	20	MD
Hobbs_1982_FC_55z_24[33]	1	UK	MD	MD	MD	unknown	no	yes	MD	Canned Tuna (3)	MD	16	MD
Hobbs_1982_FC_55z_25[33]	1	UK	MD	MD	MD	unknown	no	yes	MD	Canned Tuna (3)	MD	260	MD
Hobbs_1982_FC_55z_26[33]	2	UK	MD	MD	MD	unknown	no	yes	MD	Canned Tuna (3)	MD	6400	MD
Hobbs_1982_FC_55z_4[33]	1	UK	MD	MD	MD	unknown	no	yes	MD	Canned Mackerel (3)	MD	12.5	MD
Hobbs_1982_FC_55z_5[33]	1	UK	MD	MD	MD	unknown	no	yes	MD	Canned Pilchard (3)	MD	17	MD
Hobbs_1982_FC_55z_7[33]	1	UK	MD	MD	MD	unknown	no	yes	MD	Canned Tuna (3)	MD	>10000	MD
Hwang_1997_CB_tre_1[34]	3	MD	MD	MD	yes	unknown	no	yes	eating house	fried marlin fillet (5)	MD	MD	MD
Iguchi_2008_CB_qwe_135[35]	3	Tokio	MD	MD	no	unknown	no	yes	restaurant	sun-dried scombroid fish (5)	1	1600-5200	MD
Jantschitsch_2011_EN _80u_1[36]	2	Vienna	MD	MD	no	unknown	yes	yes	restaurant	tuna salad (3)	1	1841	MD
Jiang_2009_CB_mbc_1[37]	71	Kaohsiung City (Taiwan)	MD	MD	no	unknown	no	yes	school	fried sailfish fillet (5)	1	377.4	MD
Kanki_2004_EC_d8e_1[38]	1	Osaka, Japan	no	no	no	unknown	no	yes	probably home	sardine dried (5)	1	3000	MD

Kelso_2009_EC_80e_1[39]	1	San Diego, California	MD	MD	yes	unknown	no	yes	restaurant	grilled tuna sandwich (5)	1	2400	MD
Kim_1979_EC_71t_6[40]	1	Honolulu	MD	MD	yes	unknown	no	yes	nursing home	mahi mahi (2)	1	630	MD
Kow-Tong_1987_EC_k8r_1[41]	41	Taiwan	MD	MD	MD	unknown	no	yes	employee cafeteria	fried fish (white-tipped mackerel) (1)	1	100	MD
Leask_2004_EC_kkk_1[42]	9	South-eastern Sydney	MD	MD	no	unknown	no	yes	mobile canteen	fish curry (5)	1	2009	MD
Lee_2012_EN_ii8_1[43]	67	Kaohsiung City (Taiwan)	no	no	no	unknown	no	yes	MD	fried fish (*Tetrapturus audax*) (5)	5	348	392.07
McLauchlin_2006_EN_u_1[3]	4	London	MD	MD	MD	unknown	no	yes	restaurant	fresh tuna steaks (1)	2	3930	876.81
McLauchlin_2006_EN_u_2[3]	16	London	MD	MD	MD	unknown	no	yes	restaurant	fresh tuna steaks (1)	1	5950	MD
McLauchlin_2006_EN_u_3[3]	2	London	MD	MD	MD	unknown	no	yes	Brasserie	fresh tuna steaks (1)	1	1700	MD
Missing_name_1988_FC_97y_1[44]	2	Albuquerque	yes	MD	no	unknown	no	yes	MD	mahi mahi (2)	1	200	MD
Missing_name_2000_FC_y45_1[45]	4	Pennsylvania	MD	MD	MD	unknown	no	yes	restaurant	tuna-spinach salad (5)	1	>50	MD
Molinari_1989_EC_po1_1[46]		MD	MD	MD	MD	unknown	no	yes	MD	smoked mackerel (5)	2	1185	162.63
Muller_1992_EC_3eq_1[47]		Stellenbosch	MD	MD	MD	unknown	no	yes	restaurant or home	Grilled or fried Cape yellowtail (Seriola lalandii) (5)	1	250	MD
Muller_1992_EC_3eq_2[47]		Stellenbosch	MD	MD	MD	unknown	no	yes	restaurant or home	Grilled or fried Cape yellowtail (*Seriola lalandii*) (5)	1	720	MD
Muller_1992_EC_3eq_3[47]		Stellenbosch	MD	MD	MD	unknown	no	yes	restaurant or home	Grilled or fried Cape yellowtail (Seriola lalandii) (5)	1	1625	MD
Nalinee Hongchumpon Ouppapong_2010_EC_knv_1[48]	28	Samut Prakan Province, Thailand	MD	MD	MD	unknown	no	yes	factory kitchen and cafeteria	Fried fermented tuna (4)	1	446.2	MD
Ohnuma_2001_EC_40e_1[49]	8	Yokohama	MD	MD	no	unknown	no	yes	restaurant	yellowfin tuna (*Thunnus albacares*) sautè (1)	1	3100	MD
Predy_2003_EN_88e_1[50]	1	Edmonton (Canada)	MD	MD	yes	unknown	yes	yes	coffee shop	tuna fish salad (3)	1	350	MD
Sanchez-Guerrero_1997_EN_8U_5[51]	10	Lorca Murcia, Spain	MD	MD	MD	unknown	no	yes	grocer's shop	tuna (*Thunnus thynnus*) (5)	1	20000	MD
Sanders_1987_PC_qrs_1[52]	23	New Jersey, U.S.A.	MD	MD	yes	unknown	no	yes	monastery	yellowfin tuna broiled and boiled (2)	1	3700	MD
Schulze_1979_PC_sss_1[53]	1	Bremerhafen (Bremen harbour)	no	no	no	unknown	no	yes	MD	sardines skin and viscera free, in oil (3)	1	>500	MD

(*Continued on next page*)

Table 1. (*Continued*)

Poisoning sample id / Reference	*N*	Location	Alcohol consumption	Previous medication	Female sex	Health status	Heterogeneous food	Histamine-releasing capacities food	Source of food	Type of food (food category)	Sample size	Sample mean (mg/kg)	Sample standard deviation (mg/kg)
Sinn_2006_PC_nnn_1[54]	20	Berliner Stadtberzirk Charlottenburg-Wilmersdorf (Berlin)	no	no	no	unknown	yes	yes	school canteen	Butterfish-salmon-potato patties (5)	1	565	MD
Stell_1997_EN_efb_1[55]	1	London	MD	MD	no	unknown	no	yes	wine bar	cooked fresh tuna (1)	1	>2000	MD
Stell_1997_EN_efb_2[55]	7	London	MD	MD	no	unknown	yes	yes	MD	tuna mayonnaise sandwiches (5)	1	>2500	MD
Su_2000_PC_aae_1[56]		Pingtung County, southern Taiwan	MD	MD	MD	unknown	no	yes	public primary school	Marlin (*M. Mazara*) fried fillets (5)	12	550.78	26.56
Taylor_1982_PC_tta_1[57]	6	Portsmouth, NH, USA	MD	MD	MD	unknown	no	no	aircraft carrier canteen	swiss cheese (6)	3	1870	MD
Tsai_2005_PC_bcd_1[58]	3	Taipei Prefecture, northern Taiwan	MD	MD	MD	unknown	no	yes	grocery	Canned Mackerel (3)	3	1539	98
Tsai_2007_PC_cde_1[59]	3	Tainan Prefecture, southern Taiwan	MD	MD	MD	unknown	no	yes	grocery	Dried milkfish (*Chanos chanos*) (5)	3	616	28
Tsai_2007_PC_efg_1[60]	59	Pingtung, southern Taiwan	MD	MD	MD	unknown	no	yes	restaurant	Fried Billfish meats (*Makaira nigricans*) (5)	1	2573	MD
Tsai_2007_PC_efg_2[60]	43	Taichung, central Taiwan	MD	MD	MD	unknown	no	yes	restaurant	Frozen Billfish meats (*Xiphias gladius*) (2)	5	2022.6	413.04
Valentini_1991_PC_ccc_1[61]	3	Alta Val di Cecina (Italy)	MD	MD	MD	unknown	no	yes	canteen shop	canned tuna (3)	3	970-1050	MD
Wu_1977_PC_aar_1[62]	4	Northern Taiwan	MD	MD	yes	unknown	no	yes	fastfood store	fried fish (*Makaira spp.*) (5)	1	841.3	MD
Wu_1977_PC_aar_2[62]	48	Northern Taiwan	MD	MD	MD	unknown	no	yes	employee cafeteria	fried fish (*Euthynnus spp.*) (5)	2	1952	1084.70
missing_name_1985_EN_3g6_1[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_10[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_11[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_12[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_13[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_14[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_15[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD

missing_name_1985_EN_3g6_16[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_17[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_18[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_19[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_2[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_20[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_21[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	portuguese canned sardines (3)	1	800	MD
missing_name_1985_EN_3g6_22[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	canned tuna from Peru (3)	1	>1000	MD
missing_name_1985_EN_3g6_23[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	canned tuna from Peru (5)	1	>1000	MD
missing_name_1985_EN_3g6_24[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	smocked mackerel (5)	1	>1000	MD
missing_name_1985_EN_3g6_3[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_4[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_5[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_6[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_7[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_8[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_1985_EN_3g6_9[63]		England and Wales	MD	MD	MD	unknown	no	yes	MD	fish (5)	1	<200	MD
missing_name_2007_CB_dhi_1[64]	6	Louisiana	MD	MD	MD	unknown	no	yes	company cafeteria	tuna steaks (5)	1	<200	MD

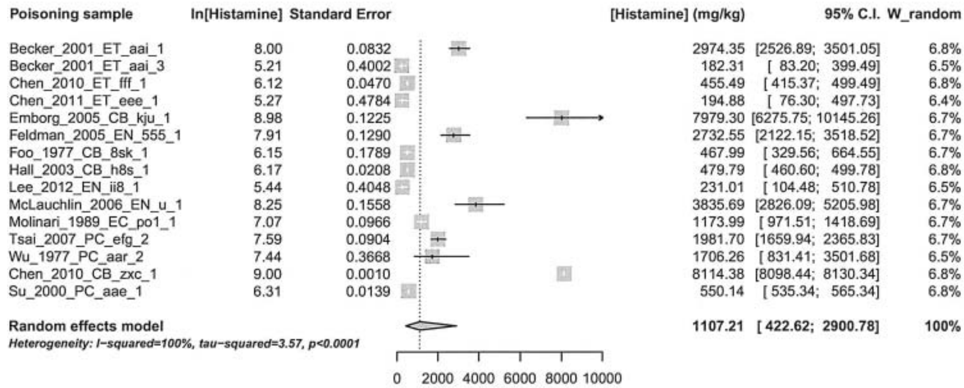

Figure 3. Meta-analysis of histamine concentration. The plot is centered on the meta-mean value. Lines are 95% confidence intervals for the means (c.i.) of the single poisoning samples. Lines with arrows indicate that plots of c.i. are truncated, due to the wide range of values. In the left size of the figure are shown values in the natural logarithm scale with their standard errors. In the right side are shown the above values transformed from log-mean and its standard error to the mean and confidence interval in the ordinary scale. At the bottom of the figure, from left to right, are shown the above items. Right: model used with main heterogeneity parameter estimates; center: scale of the values plus a polygon that plots confidence interval of the "meta-mean"; left: meta-mean and confidence interval actual values (ordinary scale).

episodes of histamine intoxication, ranged from 1 to 347 (person/poisoning sample). In these outbreaks the sources of food were reported in 50 episodes (missing = 53). On the known 50 sources, 17 were related to institutional or company food services, 20 to restaurants, and only 9 (plus 4 unsure) linked to private home. Among the 103 poisoning samples, 101 were fish and seafood and only two were cheese. The raw data for each outbreaks of histamine intoxication are presented in Table 1. The meta-analysis of data from the 52 selected articles is summarized in Forest plot (Fig. 3); the mean histamine concentration in studied episodes is 1107.21 mg/kg with a confidence interval of 422.62–2900.78 mg/kg. Heterogeneity index (I^2) was 100% ($P < 0.0001$), log-prediction interval was 3.18–10.84, equivalent to 24.12–50822.78 mg/kg. Secondary outcomes that are the concomitant conditions relevant to histamine poisoning were not evaluated, because in the most of included articles they are missing.

Risk of bias as quality score of individual reports

Quality items values and the overall quality score are presented in Table 2 for each included report.

Risk of bias across reports

No elements pointing to selective reporting bias were detected. Publication bias was not assessed.

Additional analyses

Due to the nature of results about "concomitant conditions" outcome, this was not considered for additional analyses.

Subgroup analyses

Number of poisoning samples and histamine concentration outcomes by geographic locations were not analyzed because of too many different locations.

The number of poisoning samples and histamine concentration outcomes by food categories was analyzed (respectively Table 3 and Fig. 4).

Sensitivity analyses

The following analyses were made: number of poisoning samples and histamine concentration outcomes by quality score categories; histamine concentration outcome by groups where variability was derived and where was not. Their results are respectively shown in Table 4 and Figs. 5 and 6.

Discussion

About the fish species associated with poisoning samples, it is worth noting that, n. 59 (out of 101) belonged to species associated with a high amount of histidine, according to EU legislation, that establishes a legal limit of histamine for "Particularly fish species of the families: *Scombridae, Clupeidae, Engraulidae, Coriphaenidae, Pomatomidae, Scomberosocidae."*(Communities, 2007), because these species are more likely to contain high histamine levels, as during spoilage some bacteria produce decarboxylase enzymes and convert histidine to histamine. Other 21 belonged to fish species without a legal limit in EU, and for a good 21 poisoning samples the species was unknown.

The data obtained by our review about canned tuna refute certain views that see this product as a main cause of poisoning. Among the 101 poisoning fish samples, only 22 consisted in canned products, mainly canned tuna (Table 3) and all 22 poisoning samples were related to events happened before 1985, but two (Valentini, Levre, et al., 1991; Tsai, Kung, et al., 2005).

At present, canned tuna, and other canned fish belonging to species associated with the risk of histamine, have very low levels of histamine; this fact is likely due to the quality of canning process that is improving over the years due to widespread application of HACCP principles, from the caught fish on the vessel to the processed product (Cattaneo, 2011; Guillier, Thebault, et al., 2011).

Other three episodes regarded canned tuna as ingredient (tuna salad and tuna sandwiches) (Stell, 1997; Predy, Honish,

Table 2. Quality items values and overall quality score.

Poisoning sample id / reference	Health status	Age	Sex	Source of medical diagnosis	Source of food	Histamine measurement method	Variability estimate	Quality score
Becker_2001_ET_aai_1[2]	0	1	0	0	1	0	0	3
Becker_2001_ET_aai_3[2]	0	1	0	0	1	0	0	3
Bedry_2000_EN_mi1_1[12]	0	1	1	0	0	1	0	4
Bremer_2003_ET_cca_1[13]	0	0	0	0	0	0	0	1
Bremer_2003_ET_cca_2[13]	0	0	0	0	0	0	0	1
Bremer_2003_ET_cca_3[13]	0	0	0	0	0	0	0	1
Chen_2008_ET_hhh_1[14]	0	0	0	0	0	1	1	3
Chen_2010_CB_zxc_1[15]	0	0	0	0	1	1	1	3
Chen_2010_ET_fff_1[16]	0	0	0	0	1	1	0	3
Chen_2011_ET_eee_1[17]	0	0	0	0	1	1	0	3
Chianèa_1998_ET_nnn_1[18]	0	0	0	0	1	1	0	2
D'Aloia_2011_EN_5jb_1[19]	1	1	1	0	0	0	0	4
Demoncheaux_2012_EN_99w_1[20]	1	1	1	0	1	1	1	7
Doeglas_1967_ET_vvv_1[21]	0	1	1	1	0	0	0	4
Eckstein_1999_EN_8f6_1[22]	0	0	0	0	1	1	0	3
Emborg_2005_CB_kju_1[23]	0	0	0	0	1	1	0	2
Emborg_2006_CB_kjs_1[24]	0	0	0	0	1	1	1	3
Emborg_2006_CB_kjs_2[24]	0	0	0	0	1	1	1	3
Emborg_2006_CB_kjs_3[24]	0	0	0	0	1	1	1	3
Feldman_2005_EN_555_1[25]	0	1	0	1	1	1	0	5
Fernandez_2001_CB_3jd_3[26]	0	1	1	1	1	1	0	5
Foo_1975_CB_h67_1[27]	0	0	0	0	0	1	0	1
Foo_1975_CB_jso_1[28]	0	0	0	0	0	0	0	0
Foo_1977_CB_8sk_1[29]	0	0	0	0	0	1	0	1
Gellert_1992_82c_1[30]	0	1	0	0	1	0	0	3
Guly_2006_EN79j _1[31]	0	0	0	1	1	0	0	3
Hall_2003_CB_h8s_1[32]	0	1	1	1	1	0	0	4
Hobbs_1982_FC_55z_14[33]	0	0	0	0	0	1	0	1
Hobbs_1982_FC_55z_15[33]	0	0	0	0	0	1	0	1
Hobbs_1982_FC_55z_16[33]	0	0	0	0	0	1	0	1
Hobbs_1982_FC_55z_18[33]	0	0	0	0	0	1	0	1
Hobbs_1982_FC_55z_20[33]	0	0	0	0	0	1	0	1
Hobbs_1982_FC_55z_21[33]	0	0	0	0	0	1	0	1
Hobbs_1982_FC_55z_22[33]	0	0	0	0	0	1	0	1
Hobbs_1982_FC_55z_23[33]	0	0	0	0	0	1	0	1
Hobbs_1982_FC_55z_24[33]	0	0	0	0	0	1	0	1
Hobbs_1982_FC_55z_25[33]	0	0	0	0	0	1	0	1
Hobbs_1982_FC_55z_26[33]	0	0	0	0	0	1	0	1
Hobbs_1982_FC_55z_4[33]	0	0	0	0	0	1	0	1
Hobbs_1982_FC_55z_5[33]	0	0	0	0	0	1	0	1
Hobbs_1982_FC_55z_7[33]	0	0	0	0	0	1	0	1
Hwang_1997_CB_tre_1[34]	0	0	1	0	1	1	1	4
Iguchi_2008_CB_qwe_135[35]	0	0	0	1	1	0	0	2
Jantschitsch_2011_EN_80u_1[36]	0	1	1	1	1	0	0	5
Jiang_2009_CB_mbc_1[37]	0	0	1	0	1	0	0	2
Kanki_2004_EC_d8e_1[38]	0	0	0	0	1	1	0	3
Kelso_2009_EC_80e_1[39]	0	1	1	0	1	0	0	4
Kim_1979_EC_71t_6[40]	0	1	1	0	1	0	0	4
Kow-Tong_1987_EC_k8r_1[41]	0	0	0	0	1	1	0	3
Leask_2004_EC_kkk_1[42]	0	1	1	0	1	0	0	4
Lee_2012_EN_ii8_1[43]	0	0	0	0	0	0	0	1
McLauchlin_2006_EN_u_1[3]	0	0	0	0	1	0	0	2
McLauchlin_2006_EN_u_2[3]	0	0	0	0	1	0	0	2
McLauchlin_2006_EN_u_3[3]	0	0	0	0	1	0	0	2
Missing_name_1988_FC_97y_1[44]	0	0	1	1	0	0	0	2
Missing_name_2000_FC_y45_1[45]	0	0	0	1	1	1	0	3
Molinari_1989_EC_po1_1[46]	0	0	0	0	0	1	0	1
Muller_1992_EC_3eq_1[47]	0	0	0	1	1	1	0	3
Muller_1992_EC_3eq_2[47]	0	0	0	1	1	1	0	3
Muller_1992_EC_3eq_3[47]	0	0	0	1	1	1	0	3
Nalinee Hongchumpon Ouppapong_2010_EC_knv_1[48]	0	1	1	0	1	0	0	4
Ohnuma_2001_EC_40e_1[49]	1	1	1	1	1	1	0	7
Predy_2003_EN_88e_1[50]	1	1	1	1	1	0	0	6
Sanchez-Guerrero_1997_EN_8U_5[51]	0	0	0	0	1	0	0	2
Sanders_1987_PC_qrs_1[52]	0	0	1	0	1	0	0	3
Schulze_1979_PC_sss_1[53]	0	0	0	0	0	1	0	2
Sinn_2006_PC_nnn_1[54]	0	0	0	0	1	0	0	2
Stell_1997_EN_efb_1[55]	0	1	1	0	1	0	0	4
Stell_1997_EN_efb_2[55]	0	0	0	0	0	0	0	1
Su_2000_PC_aae_1[56]	0	0	0	0	1	1	1	4

(*Continued on next page*)

Table 2. (*Continued*)

Poisoning sample id / reference	Health status	Age	Sex	Source of medical diagnosis	Source of food	Histamine measurement method	Variability estimate	Quality score
Taylor_1982_PC_tta_1[57]	0	0	0	0	1	1	0	3
Tsai_2005_PC_bcd_1[58]	0	0	0	0	1	1	1	4
Tsai_2007_PC_cde_1[59]	0	0	0	0	1	1	1	4
Tsai_2007_PC_efg_1[60]	0	0	0	0	1	1	0	3
Tsai_2007_PC_efg_2[60]	0	0	0	0	1	1	0	3
Valentini_1991_PC_ccc_1[61]	0	0	0	0	1	1	0	3
Wu_1977_PC_aar_1[62]	0	0	1	1	1	1	0	5
Wu_1977_PC_aar_2[62]	0	0	0	0	1	1	0	3
missing_name_1985_EN_3g6_1[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_10[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_11[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_12[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_13[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_14[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_15[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_16[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_17[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_18[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_19[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_2[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_20[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_21[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_22[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_23[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_24[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_3[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_4[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_5[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_6[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_7[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_8[63]	0	0	0	0	0	0	0	0
missing_name_1985_EN_3g6_9[63]	0	0	0	0	0	0	0	0
missing_name_2007_CB_dhi_1[64]	0	0	0	0	1	0	0	1

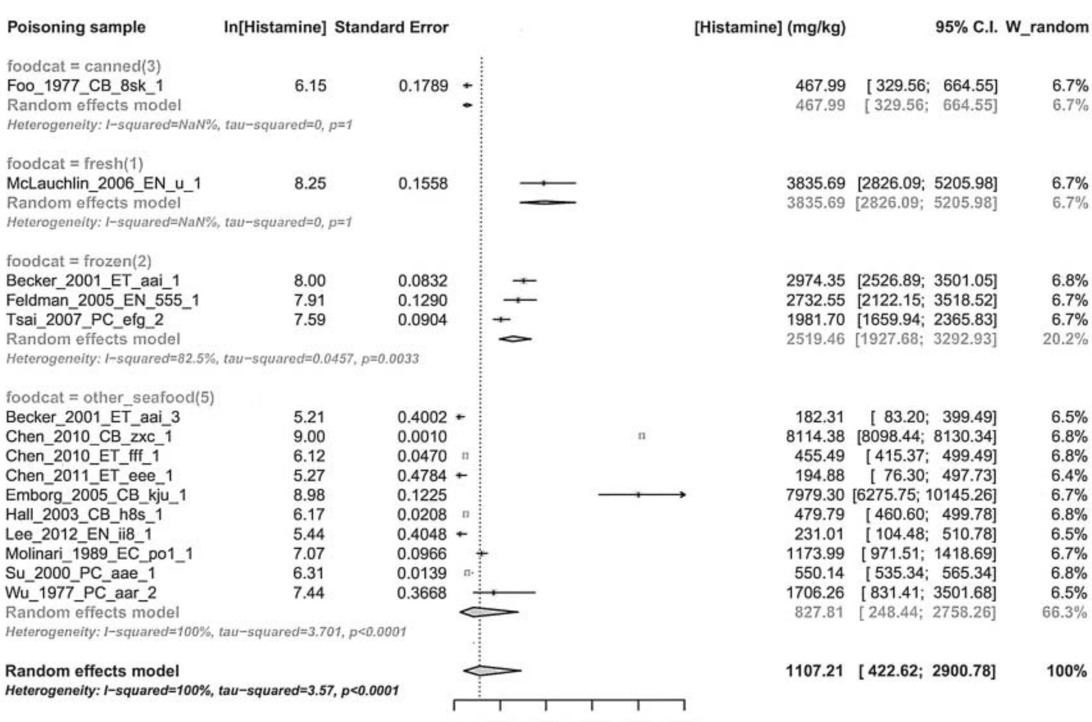

Figure 4. Sub-group analysis: Meta-analysis of histamine concentration by food category. Four meta-analyses plots, each corresponding to one food category ("foodcat") are stacked vertically. The items present in each plot are the same of Fig. 3 plot and are explained in Fig. 3 caption.

Table 3. Sub-group analysis: Number of poisoning samples by food category.

Food category id	Food category	Number of poisoning samples	Percent
1	Fresh	9	8.74
2	Frozen	7	6.80
3	Canned	22	21.36
4	Fermented	1	0.97
5	Other seafood	62	60.19
6	Cheese	2	1.94
7	Other foods	0	0.00
Totals	All categories	103	100.00

Table 4. Sensitivity analysis: Number of poisoning samples by quality score.

Quality score	Number of poisoning samples	Percent
0	25	24.27
1	23	22.33
2	11	10.68
3	24	23.30
4	13	12.62
5	4	3.88
6	1	0.97
7	2	1.94
Totals	103	100.00

et al., 2003; Jantschitsch, Kinaciyan, et al., 2011). In all three, tuna cans had been opened hours or even a week before the preparation or the consumption, with likely post-processing contamination and consequent histamine production.

Fresh or frozen fish, diversely prepared and cooked, and fish products differently processed (not canned) were cause of poisoning in 79 episodes. The species or the family mainly reported were (number, % of 79): tuna (26, 32.9%); scombridae other than tuna (7, 8.8%); mahi mahi (3, 3.8%); species of the family *Istiophoridae* (total 8, 10.1%) such as *Makaira* spp (5), *Tetrapturus* spp (2), sailfish (1); swordfish (2); others species (12, 15.2%).

Among the "others," *Seriola lalandi* (n.3), *Chanos chanos* (n.1), *Arripis trutta* (n.4) were reported, fish species not considered in EU legislation, while having very high concentrations of histidine. Three other outbreaks (Eckstein, Serna, et al., 1999; Feldman, Werner, et al., 2005; Sinn, 2006) were attributed to *Lepidocybium flavobrunneum*, species whose meat has a very high content of wax ester that could cause gastrointestinal effects, but also has histidine levels as high as many Scombridae.

As to *Istiophoridae* and *Xiphidae* families, suborder Xiphiodei, in other countries they are associated with the risk of histamine because known to have very high free histidine levels or to be associated with SFP (Scombrotoxin Fish Poisoning) (F.A. O., 2014). Interestingly, the family *Istiophoridae* (Billfish) is placed in the Scombroidei suborder by Nelson (2006). Both Billfish and scombrids have common characteristics that could explain the frequency of episodes of histamine intoxication caused by billfish. The complete list of fish species produced by our review can help to control imports and medical history of cases of suspected poisoning, as well as to cope with the problems arising from changes in international market trends of fishery products.

The source of poisoning (places where the poisoning samples were eaten) was not reported in 53 episodes (out of 103). The main reported sources were restaurants (20 cases, plus 3 unsure) and institutional foodservice, company or community canteens and cafeterias (17 cases), where the number of people involved is in terms of dozens or hundreds. The outbreaks occurred at home were 9 (plus 4 unsure); probably this kind of poisoning, involving a small number of persons for single episode, is little reported in the literature and could indicate a reporting bias (under-reporting).

Regarding the result of meta-analysis, the meta-mean of histamine concentration that summarizes the 14 reports (Foo, 1977; Molinari, Montagnoli, et al., 1989; Wu, Yang, et al., 1997; Su, Chou, et al., 2000; Becker, Southwick, et al., 2001; Hall, 2003; Emborg, Laursen, et al., 2005; Feldman, Werner, et al., 2005; Mclauchlin, Little, et al., 2006; Tsai, Hsieh, et al., 2007; Chen, Huang, et al., 2010; Chen, Lee, et al., 2011; Lee, Huang,

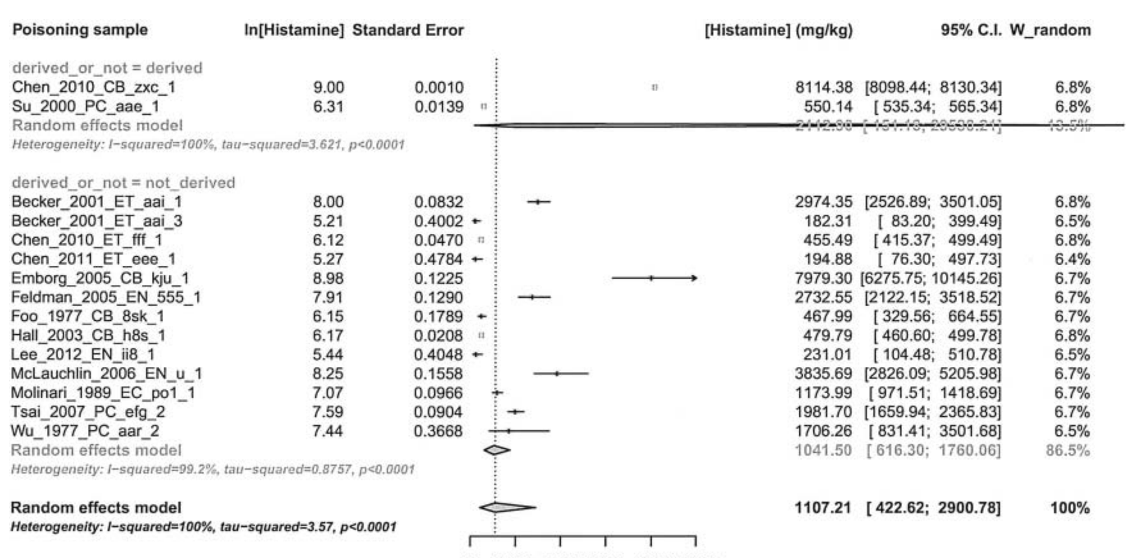

Figure 5. Sensitivity analysis: Meta-analysis of histamine concentration by variability derived or not. The two plots, one for variability derived data and the other for those not derived, are stacked vertically. Please refer to previous figures captions for explanations of plot items.

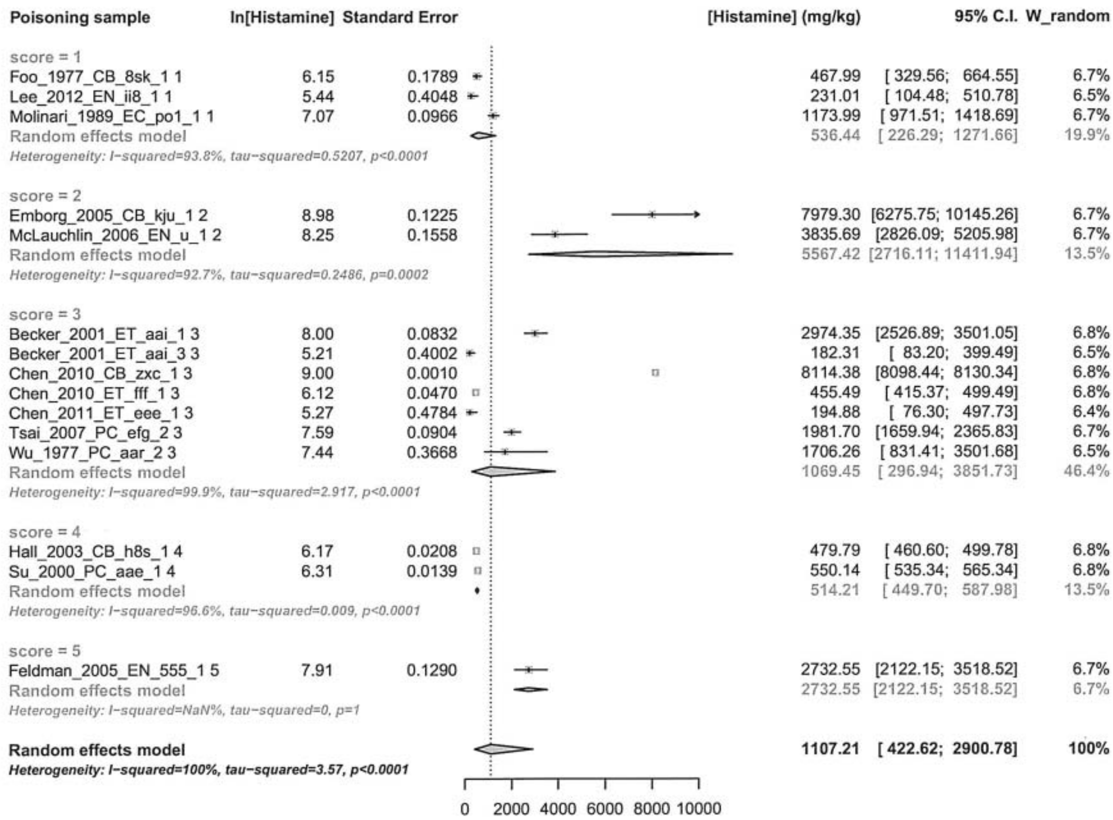

Figure 6. Sensitivity analysis: Meta-analysis of histamine concentration by quality score. The plots of the quality score categories meta-analyses are stacked vertically. Please refer to previous figures captions for explanations of plot items.

et al., 2012) used for the statistical calculation (Fig. 3) is about 1000 ppm, a very high value if compared with what assumed by FDA (F.D.A., 2014) indicating, in most cases, histamine levels in illness-causing fish of about 200 or 500 ppm. On the other side, our result is in agreement with McLaughlin et al. (Mclauchlin, Little, et al., 2006) who wrote that ingestion of fish containing histamine at levels around 1000 ppm can result in illness. Shalaby (1996) emphasized that poisoning does occur at histamine concentrations lower than 100 mg/100 g and levels of histamine in fish of 5–20 mg/100 g (50–200 ppm) are possibly toxic. This could be congruent with the lower limit of overall predictive interval of histamine concentration from meta-analysis (24.12 ppm) although, due to the highest heterogeneity amount estimated, this value is questionable. Either way, EU maximum limit (Communities, 2007) seems to be proper to protect the consumer, also respect to the meeting report of FAO/WHO (F.A.O., 2014), where an oral NOAEL (No Observed Adverse Effect Level) of 50 mg was identified, from which was derived a histamine limit of 200 mg/kg, considering a service size of 250 g.

Due to the highest (100%) level of heterogeneity estimated for the overall meta-analysis the limits both for the meta-mean confidence interval and the predictive interval are questionable. More reliable are the values for subgroups, where moderate amount of heterogeneity was estimated.

Subgroup analysis of histamine concentration outcome by food categories did not show significant difference between subgroups due to the overlapping of confidence interval. Moreover, the food category "fermented" (4) is missing, while categories "fresh" (1) and "canned" (3) consist of only one record and food category "other seafood" (5) is highly heterogeneous.

Sensitivity analysis of histamine concentration outcome by quality categories did not show separation of the values of quality categories (overlapping of confidence interval) but this cannot lead to declare absent the quality category effect, due to remarkable difference between the means of the categories, high degree of heterogeneity of each category and finally presence of single-record categories.

About sensitivity analysis of histamine concentration by derived or not variability, also this is poorly interpretable, due to high heterogeneity amount in each group and very unbalanced sample size of the two groups (2 vs. 13). Moreover, the overlapping of confidence intervals is scarcely meaningful because it is very large value in "variability derived" category.

Single-specimen poisoning samples were excluded from histamine concentration meta-analysis in order to not confound within—and between specimen variability.

Conclusions

The main goal of our systematic review was to remove noise as more as possible from information about values of histamine in foods involved into poisoning; this goal has been reached by producing objective estimates.

To attribute precisely the responsibility of the poisoning event, increasing knowledge, allowing the food business operators to improve their practice or processing, as well as guaranteeing the customer also legally, it is fundamental to approach this topic with pragmatism. We hope that these estimates could be a valid reference for operators and consumers.

The estimate of the mean was found to be fairly high, its precision was unfortunately impaired by a lot of variability (heterogeneity).

Too few suitable data are presently available to conduct a reliable analysis on homogeneous subsets of food.

It is recommended that histamine poisoning episodes are recorded and published including the values of all important variables pointed out in this review, moreover, the variability within poisoning sample should be stated analyzing at least twice the histamine content for each sample. About the conditions concomitant to the poisonings, the role of several health conditions, drugs and meal composition on the proceeding of an event of histamine (scombroid) poisoning has been underlined several times (Sattler, Hesterberg, et al., 1985; Taylor, 1986; Maintz, Novak, 2007; Hungerford, 2010). Alcoholic beverages can increase the seriousness of the episodes enhancing the absorption of histamine contained in the meal, but even if the importance of alcohol is reported in a previous review (Lehane, Olley, 2000) and other reports (Geiger, 1955; Zee, Simard, et al., 1981; Zimatkin, Anichtchik, 1999; Maintz, Novak, 2007), our results point out lack of this information, so it is recommended to physicians to include such items in the anamneses of the poisoning cases.

Contributions of authors

CB building protocol, study selection, data extraction and writing review; EC bibliographic search; FC building protocol, study selection, data extraction and analysis and writing review; PC: building protocol, supervising of all phases and writing review.

Declarations of interest

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Table A. Characteristics of searched database.

Database category (some database belong to more than one category, in this case a semicolon (";") is used to separate multiple categories)	Database name	Database time interval	Database-specific search strategy(sometimes three contiguous underscores "___" are used to separate search steps or multiple searches–this symbol doesn't belong to search strategy syntax; moreover sometimes, due to syntax complexity, only the main structure of search is reported)	Final number of items retrieved from database
Dissertations and theses database	DART EUROPE	—	Keywords = histamine poisoning Keywords = histamine intoxication Keywords = "scombroid syndrome"	1
	ProQuest Dissertation & Theses Database	—	histamine AND (poisoning OR intoxication) OR "scombroid syndrome"	0
Full text journals available electronically	BioMed Central	1997–2013	((histamine AND (poisoning OR intoxication)) OR scombroid and syndrome and (Exact and phrase) and in and All and fields and (full and text)) (All words) in All fields (full text) from 1997 to 2013 ___ 13 (All words) in All fields (full text) from 1997 to 2013 ___ (histamine AND (poisoning OR intoxication)) OR scombroid syndrome (Exact phrase) in All fields (full text) (All words) in All fields (full text) ___ histamine AND (poisoning OR intoxication) (All words) in All fields (full text) ___ poisoning OR intoxication (All words) in All fields (full text) ___ scombroid syndrome (Exact phrase) in All fields (full text) ___ intoxication (All words) in All fields (full text) ___ poisoning (All words) in All fields (full text) ___ histamine (All words) in All fields (full text) from 1997 to 2013	0
	HighWire Press	01/01/1959–31/12/2013	(histamine and poisoning) or (histamine and intoxication) or "scombroid syndrome"	15
	PubMed Central (PMC)	01/01/1959 –31/12/2013	((((("Histamine/poisoning"[Mesh] OR "Histamine/toxicity"[Mesh]) AND (Humans [Mesh]))) OR ("scombrotoxin"[Supplementary Concept] OR "saurine"[Supplementary Concept]))) OR ((("Biogenic Amines/agonists"[Mesh] OR "Biogenic Amines/poisoning"[Mesh] OR "Biogenic Amines/toxicity"[Mesh])) AND ("Histamine"[Mesh]) AND (Humans[Mesh])) AND (Humans[Mesh])	51
General bibliographic database	CENTRAL	1959–2012	#1 MeSH descriptor: [Biogenic Amines] explode all trees ___ #2 #1 from 1959 to 2012, in Trials ___ #3 #1 or #2 from 1959 to 2012, in Trials ___ #4 "scombroid fish poisoning" or "scombroid food poisoning" or "scombroid poisoning" or "scombroid syndrome" or "scombroid type poisoning" or "scombroide intoxicatie" or "scombrotoxic" or "scombrotoxic fish" or "scombrotoxic fish poisoning" or "scombrotoxic poisoning" or "scombrotoxicosis" or "scombrotoxin" or "scombrotoxin poisoning" or "scombrotoxins" from 1959 to 2012, in Trials ___ #5 "histamine poisoning"or "histamine intoxication" from 1959 to 2012, in Trials ___ #6 #3 or #4 or #5 from 1959 to 2012, in Trials ___ #7 MeSH descriptor: [Foodborne Diseases] explode all trees ___ #8 "food poisoning" from 1959 to 2012, in Trials ___ #9 #7 or #8 from 1959 to 2012, in Trials ___ #10 #6 and #9 from 1959 to 2012, in Trials ___ #11 MeSH descriptor: [Food] explode all trees ___ #12 food ___ #13 #11 or #12 from 1959 to 2012, in Trials ___ #14 MeSH descriptor: [Fishes] explode all trees ___ #15 fish ___ #16 #14 or #15 from 1959 to 2012, in Trials ___ #17 #13 or #16 ___ #18 #10 and #17	1
	Cinahl	01/01/1959–31/12/2013	S1 (MH "Histamine/PO") ___ S2 (MH "Histamine") ___ S3 (MH "Toxicology") OR (MH "Toxins+") ___ S4 scombrotoxin* ___ S5 biogenic* ___ S6 S1 OR S4 ___ S7 (S6) OR (S2 AND S3) ___ S8 (S5) AND (S2) ___ S9 S7 ___ S10 (S7) OR (S8) ___ S11 (MH "Poisoning+") OR TI POISON* ___ S12 (S2 AND S11) ___ S13 S10 OR S12	24
	FSTA (Food Science and Technology Abstracts)	1959–Current	1. scombroid poisoning/ ___ 2. histamine/ ___ 3. poisoning/ ___ 4. FOOD POISONING/ ___ 5. exp toxicity/ ___ 6. (POISON* or TOXIC*).hw,ti. ___ 7. HISTAMINE.ti. ___ 8. 6 and 7 ___ 9. 3 or 4 or 5 ___ 10. 2 and 9 ___ 11. 1 or 8 or 10 ___ 12. saurine.hw,ti. ___ 13. 11 or 12	82
	SciFinder	1959–2012	Main structure of search: #1 "biogenic amines."to ___ #2 "scombroid syndrome" ___ #3 "histamine poisoning" ___ #4 #1 or #2 or #3 ___ #5 "food poisoning" ___ #6 #4 and #5 ___ #7 food ___ #8 fish ___ #9 #7 or #8 ___ #10 #6 and #9	0

	Scirus	1950–2013	("food poisoning" and ("biogenic amines" or "scombroid syndrome" or "scombroid fish poisoning" or "scombroid food poisoning" or "scombroid poisoning" or "scombroid syndrome" or "scombroid type poisoning" or "scombroide intoxicatie" or scombrotoxic or "scombrotoxic fish" or "scombrotoxic fish poisoning" or "scombrotoxic poisoning" or scombrotoxicosis or scombrotoxin or "scombrotoxin poisoning" or scombrotoxins or "scombroid toxin" or "histamine poisoning" or "histamine intoxication")) and (food or fish)	87
	Scopus	>1958 & = 2013	(TITLE(scromboid* OR scrombotox*)) OR (INDEXTERMS(scombrotox* OR scombroid*)) OR (TITLE(scombrotox* OR scombroid*)) OR (TITLE(histamine) AND TITLE(poison* OR toxic*))	83
General bibliographic database; Conference abstracts or proceedings	Pubmed	01/01/1959–2013/12/31	((((("Histamine/poisoning"[Mesh] OR "Histamine/toxicity"[Mesh]) AND (Humans [Mesh]))) OR ("scombrotoxin"[Supplementary Concept] OR "saurine"[Supplementary Concept]))) OR ((("Biogenic Amines/agonists"[Mesh] OR "Biogenic Amines/poisoning"[Mesh] OR "Biogenic Amines/toxicity"[Mesh])) AND ("Histamine"[Mesh]) AND (Humans[Mesh])) AND (Humans[Mesh])	102
	Web of Science	1985–01–01–2012–11–05	ti = histamine ____ Databases = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan = All Years ____ Lemmatization = On ____ ti = (toxic* or poison*) ____ Databases = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan = All Years ____ Lemmatization = On ____ #2 AND #1 ____ Databases = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan = All Years ____ Lemmatization = On ____ ti = (biogen* and amin*) ____ Databases = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan = All Years ____ Lemmatization = On ____ #4 AND #2 ____ Databases = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan = All Years ____ Lemmatization = On ____ ti = ((scombr* and (poison* or toxic* or syndro*)) or scombrotox* or saurine) ____ Databases = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan = All Years ____ Lemmatization = On ____ #6 OR #3 ____ Databases = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan = All Years ____ Lemmatization = On ____ #7 OR #5 ____ Databases = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan = All Years ____ Lemmatization = On	54
General bibliographic database; Other reviews, guidelines and reference lists as sources of studies	Embase	<1966–2013	histamine:ti AND (poison*:ti OR toxic*:ti) OR scombroid:ti OR scombrotox*:ti AND [embase]/lim	151
General bibliographic database; Subject-specific bibliographic database	Google scholar	1959–2013	The following 4 searches were performed and their results combined A[1959–2000] = food "biogenic amines" OR "scombroid syndrome" OR "histamine poisoning" "food poisoning" ____ ____ A[2001–2012] = food "biogenic amines" OR "scombroid syndrome" OR "histamine poisoning" "food poisoning" ____ ____ B [1959–2000] = (fish "biogenic amines" OR "scombroid syndrome" OR "histamine poisoning" "food poisoning") ____ B [2001–2012] = (fish "biogenic amines" OR "scombroid syndrome" OR "histamine poisoning" "food poisoning")	180
Grey literature database		—	The following 2 searches were performed and their results merged: histamine and (poisoning or intoxication)"scombroid syndrome"	0
	EAGLE (Open Grey)	1959-2013	((histamine AND (poisoning OR intoxication)) OR "scombroid syndrome"	0
	The National Technical Information Service (NTIS)	1964-2013	The following 2 searches were performed and their results merged:histamine and (poisoning or intoxication)"scombroid syndrome"	3

(*Continued on next page*)

Table A. (*Continued*).

Database category (some database belong to more than one category, in this case a semicolon (";") is used to separate multiple categories)	Database name	Database time interval	Database-specific search strategy(sometimes three contiguous underscores "___" are used to separate search steps or multiple searches–this symbol doesn't belong to search strategy syntax; moreover sometimes, due to syntax complexity, only the main structure of search is reported)	Final number of items retrieved from database
Other reviews, guidelines and reference lists as sources of studies	Medline (Ovid)	1959-2013	exp histamine/ ___ ___ histamine.mp. ___ ___ 1 or 2 ___ exp poisoning/ ___ ___ poisoning.mp. ___ ___ 4 or 5 ___ intoxication.mp. ___ ___ intoxication. mp. ___ ___ 7 or 8 ___ 6 or 9 ___ 3 and 10 ___ 'scombroid syndrome'.mp. ___ 'scombroid syndrome'.mp. ___ 12 or 13 ___ ___ 11 or 14 ___–___ ___ ___ ___ 16 limit 15 to "review articles" ___ 17 'systematic review'.mp. ___ 18 16 and 17 ___–___ 19 18 ___ 20 limit 19 to yr = "1959 -Current"	0
	The cochrane library	1959-2013	#1 MeSH descriptor: [Histamine] explode all trees and with qualifiers: [Poisoning–PO] ___ #2 MeSH descriptor: [Histamine] explode all trees and with qualifiers: [Toxicity–TO] ___ #3 scombrotox*:ti (Word variations have been searched) ___ #4 saurine:ti,ab,kw (Word variations have been searched) ___ #5 MeSH descriptor: [Biogenic Amines] explode all trees and with qualifiers: [Poisoning–PO] ___ #6 MeSH descriptor: [Biogenic Amines] explode all trees and with qualifiers: [Toxicity–TO] ___ #7 MeSH descriptor: [Histamine] explode all trees ___ #8 (((#5 or #6) and #7) or #3 or #2 or #1) ___ #9 scombroid:ti,ab,kw (Word variations have been searched)	0
	African Index Medicus	—	. histamine and poisoning. histamine and intoxication."scombroid syndrome"	0
	FAO	1959-2013	((histamine AND (poisoning OR intoxication)) OR "scombroid syndrome"	0
	Index Medicus for the South-East Asia Region (IMSEAR)	—	. histamine and poisoning ___. histamine and intoxication ___."scombroid syndrome"	2
	IndMED	—	. histamine and poisoning ___. histamine and intoxication ___."scombroid syndrome"	0
	KoreaMed	—	. histamine and poisoning. histamine and intoxication."scombroid syndrome"	0
	LILACS	1959-2013	Sintassi LILACS ___ MH biogenic amines and (PD 1959 or PD 196$ or PD 197$ or PD 198$ or PD 199$ or PD 200$ or PD 2010 or PD 2011 or PD 2012 or PD 2013) ___ [scombroid syndrome or scombroid fish poisoning or scombroid food poisoning or scombroid poisoning or scombroid syndrome or scombroid type poisoning or scombroide intoxicatie or scombrotoxic or scombrotoxic fish or scombrotoxic fish poisoning or scombrotoxic poisoning or scombrotoxicosis or scombrotoxin or scombrotoxin poisoning or scombrotoxins or scombrotoxin] ___ ___ and (PD 1959 or PD 196$ or PD 197$ or PD 198$ or PD 199$ or PD 200$ or PD 2010 or PD 2011 or PD 2012 or PD 2013) ___ TI histamine and TI poisoning and (PD 1959 or PD 196$ or PD 197$ or PD 198$ or PD 199$ or PD 200$ or PD 2010 or PD 2011 or PD 2012 or PD 2013) ___ #1 ___ MH food poisoning or (TI food and TI poisoning) and (PD 1959 or PD 196$ or PD 197$ or PD 198$ or PD 199$ or PD 200$ or PD 2010 or PD 2011 or PD 2012 or PD 2013) ___ #1 and # 5 ___–___–___–___ -	0
	Panteleimon	—	1 ___ Keywords: histamine ___ 2 ___ Keywords: poisoning ___ 3 ___ Keywords: intoxication ___ 4 ___ Keywords: "scombroid syndrome" ___ 5 ___ Keywords: scombroid syndrome ___ 6 ___ Комбінація: 1 1 AND 2 ___ 7 ___ Комбінація: 1 1 AND 3 ___ 8 ___ Комбінація: 4 4 OR 5 OR 6 OR 7	0
Regional/National bibliographic database	Western Pacific Region Index Medicus (WPRIM)	1959-2013	4 #3 or #2 or #1___ 3 All:"scombroid syndrome" -Limits:1959-2013___ 2 All: histamine and All:intoxication -Limits:1959-2013___ 1 All:histamine and All: poisoning -Limits:1959-2013	0

Subject-specific bibliographic database	BiblioMap–EPPI-Centre database of health promotion research	—	1 Freetext: histamine ____ 3 Freetext: poisoning ____ 5Freetext: intoxication ____ 10 Freetext: "scombroid syndrome" ____ 11 3 OR 5 ____ 12 1 AND 11 ____ 13 10 OR 12	0
	Database of Promoting Health Effectiveness Reviews (DoPHER)	—	1 Freetext: histamine ____ 3 Freetext: poisoning ____ 5 Freetext: intoxication ____ 7 Freetext: "scombroid syndrome" ____ 8 1 AND 5 ____ 9 1 AND 3 ____ 10 7 OR 8 OR 9	0
	Global Health	—	(histamine AND poisoning) AND "scombroid syndrome" or (histamine AND intoxication) AND "scombroid syndrome"	0
	Intute	?-july 2011	. histamine and poisoning or. histamine and intoxication or."scombroid syndrome"	0
	POPLINE (reproductive health) (free on the internet)	1959-2013	histamine AND poisoning or histamine AND intoxication or "scombroid syndrome" <limit_to_years_1959-2013>	0
	Turning Research into Practice (TRIP) database	1959-2013	#4 ____ (#1 or #2 or #3)____ #3 ____ ("scombroid syndrome") from:1959 to:2013____ #2 ____ (histamine poisoning) from:1959 to:2013____ #1 ____ (histamine intoxication) from:1959 to:2013	16