ANSES Opinion
Request No 2018-SA-0026
Related Request No. 2010-SA-0195

The Director General

Maisons-Alfort, 10 July 2019

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on "Updating the method for determining causality in reports of adverse effects in nutrivigilance"

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are published on its website. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 10 July 2019 shall prevail.

On 12 February 2018, ANSES issued an internal request to update the method of determining causality in reports of adverse effects in nutrivigilance.

1. BACKGROUND AND PURPOSE OF THE REQUEST

The French Act on Regional Health Governance (2009-879) of 21 July 2009 tasked ANSES with "implementing the vigilance scheme for novel foods, food supplements, foods to which substances have been added for nutritional or physiological purposes and products intended for particular nutritional uses".

The purpose of this health surveillance scheme, which is part of the French health and safety system, is to improve consumer health by rapidly identifying any acute adverse effects linked to the consumption of these foods, in order to recommend the implementation of corrective or preventive measures by decision-makers.

The national nutrivigilance scheme relies on health professionals (mainly physicians and pharmacists), manufacturers, distributors and individuals, who contact ANSES[1] to report any adverse effects[2] potentially caused by the consumption of food supplements or, more broadly, any other food covered by the law.

[1] Directly on the ANSES website (www.anses.fr) or via the Adverse Health Event Reporting Portal put in place by the Ministry of Health (signalement.social-sante.gouv.fr)

[2] In compliance with Article R1323-3 of the public health code, "the term adverse effect refers to any harmful reaction occurring in humans under normal conditions of use of the food, or resulting from use that does not comply with purpose, with normal use or with the instructions for use or special precautions for use specified on the labelling".

Novel foods are defined in European regulation (EU) No. 2015/2283. They are foods or ingredients that were not widely consumed in the member states of the European Union before 15 May 1997 and that have one or more of the following characteristics: a new primary molecular structure or one that has been deliberately modified; food consisting of or isolated from microorganisms, fungi, algae, plants, animals or materials of mineral origin; food produced using a process that is not frequently employed, where that process brings about significant changes in their nutritional value, metabolism or content in undesirable substances. Before marketing authorisation is granted, novel foods are subject to a risk assessment by the European Food Safety Authority (EFSA).

At EU level, **food supplements** are defined by European Directive No. 2002/46/EC, transposed into French law by decree 2006/352 of 20 March 2006, as "foods intended as a supplement to the regular diet and which are a concentrated source of nutrients or other substances which alone or combined have a nutritional or physiological effect, marketed in the form of doses".

The composition and marketing of food supplements are governed by decree No. 2006/352. Positive lists of ingredients that can be used in the composition of food supplements have been drawn up for vitamins and minerals (Ministerial Order of 9 May 2006), for substances with nutritional or physiological purposes (Ministerial Order of 26 September 2016) and for plants and plant preparations (Ministerial Order of 24 June 2014). Food supplements fall under the consumer code and do not require prior individual authorisation for marketing. However, they must be declared to the Directorate General for Competition, Competition, Consumer Affairs and Fraud Control (DGCCRF), with details of their composition, in particular. Manufacturers are responsible for ensuring that products brought to market comply with applicable standards, that they are safe, and that they do not mislead consumers.

Foods to which substances have been added for nutritional or physiological purposes (vitamins, minerals or other substances such as amino acids or plant extracts) are governed by European Regulation (EC) No.1925/2006.

Food for specific nutritional uses is covered by European Regulation (EU) No. 609/2013. Examples include infant formula and food for young children, food for special medical purposes and total diet replacement food for weight control.

In the same way as for other French vigilance schemes, and given the gravity of the consequences in terms of health and the resulting manufacturing decisions, an appropriate and objective method of analysis is required to analyse the relationship of causality between a product concerned by the national nutrivigilance scheme and the adverse effect reported. Referred to as the "method of determining causality in nutrivigilance", this method assesses the degree of causality of one or more products in the occurrence of the adverse effect reported, as part of a standardised approach designed to resolve any differences in opinion that may exist between observers.

Methods of this type are frequently implemented in France for drugs (Arimone *et al.* 2011, Bégaud *et al.* 1985, Montastruc *et al.* 2005), cosmetics (Afssaps 2009) or xenobiotics in the event of intoxication (CCTv 2015).

Given the significant differences compared with drugs (no demonstrated benefit or safety study), ANSES issued an internal request on 25 August 2010 to develop a method of determining causality specific to reports of adverse effects likely to be linked to the consumption of products concerned by the national nutrivigilance scheme. This method of determining causality was published on 11 May 2011 (Anses 2011).

Since 2011, this method has been supplemented and detailed throughout its application by the "Nutrivigilance" Working Group. These details are recorded in a "manual of decisions", which has not been published.

Against this backdrop, ANSES issued an internal request on 12 February 2018 to update the method of determining causality in reports of adverse effects in nutrivigilance, taking into account the changes submitted by the Working Group since 2011.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in Expert Appraisals – General Requirements of Competence for Expert Appraisals (May 2003)".

The issues appraised fall within the scope of the Expert Committee (CES) on "Human Nutrition". ANSES tasked the "Nutrivigilance" Working Group with this appraisal. The methodological and scientific aspects of the work were presented to the CES. They were adopted by the CES on "Human Nutrition" at its meeting on 10 January 2019.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.
The experts' declarations of interests are made public via the ANSES website (www.anses.fr).

A test to establish concordance between assessors was carried out on the first version of the updated method of determining causality. This test involved ten assessors (six physicians with expertise in the method of determining causality and four physicians with no expertise in the method of determining causality), who analysed the same 30 cases. As some cases involved several products, the number of causalities analysed was 37 per assessor. These cases were selected to cover a significant number of the specialities and specific situations likely to be encountered in nutrivigilance. Concordance was measured using the Fleiss Kappa score (Fleiss 1971). Test results made it possible to fine-tune and clarify the method of determining causality by analysing the discrepancies observed.

3. ANALYSIS AND CONCLUSIONS OF THE WG AND THE CES

The method of determining causality in nutrivigilance is designed to provide the basis for an objective and reproducible assessment of the relationship of causality between a product concerned by the national nutrivigilance scheme and the adverse effect reported to ANSES.

It will be applied by the ANSES Nutrivigilance Unit as well as by the experts mandated by the Agency to analyse reports of adverse effects in nutrivigilance. It will also be brought to the attention of the competent authorities, health professionals and manufacturers, and made public.

The method of determining causality in nutrivigilance makes it possible to establish an intrinsic causality score and an extrinsic causality score.

The **intrinsic causality score** is based on the combination of two scores, one chronological, the other aetiological. This score comprises five levels of causal relationship: excluded, unlikely, possible, likely and very likely.

The **extrinsic causality score** is based on the knowledge available in scientific literature relating to the adverse effects of each ingredient in the products analysed. This score comprises three levels, based on the quality of the science demonstrating a causal effect between an ingredient and an adverse effect (not documented, little documented, well documented).

The intrinsic causality score and extrinsic causality score of adverse effects are independent of each other.

Implementation of this method:

- is possible only if the person making the report supplies the necessary information on the consumer (i.e., sex, age), the product(s) concerned (i.e., name, dates of consumption) and the adverse effects reported (i.e., description, date or onset time);
- is more pertinent if the information on each case is as detailed as possible: quantity and frequency of consumption, consumer history, ongoing treatment, objective and quantified description of the adverse effects, medical or biological test results, progression in the adverse effects and their treatment (through self-medication or on medical prescription);
- requires specialist medical expertise.

3.1 Intrinsic causality score

The intrinsic causality score:

- must be established independently for each product consumed, concerned by the nutrivigilance scheme;
- must be established separately for each symptom or syndrome if a product is suspected of causing several reactions.

Product composition must not be taken into account in establishing the intrinsic causality score. This is because:

- a level of uncertainty is possible concerning the real composition of food supplements;
- the studies available are insufficient, with respect to the kinetics and mechanisms of action of many ingredients and the way in which they interact with each other or with other foods or drugs;
- the presence of ingredients that are known to cause adverse effects may result in a tendency to under-estimate the responsibility of the other ingredients.

The intrinsic causality score is the combined result of a **chronological score** and an **aetiological score**.

3.1.1 Chronological score

The chronological score refers to the time taken for the adverse effect to appear, its progression and its recurrence when the product is reintroduced.

3.1.1.1 Onset time

If no information is available on the time taken for the adverse effect to occur in relation to the period of product consumption (time unknown), it is impossible to estimate the chronological score and, in consequence, the intrinsic score.

The onset time of the adverse effect reported may be:

- **Incompatible**, when the adverse effect occurs before the product is taken or outside the expected time frame (i.e., the time between the first intake of the product and the appearance of the adverse effect is either too short or too long). When the time is incompatible, no assessment is made of the other chronological and aetiological criteria, and the intrinsic causality score is set at 10 (excluded).
- If the onset time is **not incompatible**, it may be:
    - **Compatible,** when the adverse effect occurs within the time frame expected for the occurrence of a reaction of this type, following the ingestion or increase in the ingested dose of a causal agent;
    - **Potentially compatible,** when the adverse effect occurs within a time frame that is atypical but nevertheless possible for the effect considered.

Specific case of biological test results

In cases where biological disturbances are observed during an examination carried out within a known time frame after the start of product consumption but where no examination prior to the start of consumption is available:

- if the biological disturbance is likely to be linked to the symptoms leading to the examination, the time frame is considered to be compatible;
- if the biological disturbance is discovered by chance in an asymptomatic individual: the time frame is uncertain and therefore only considered as potentially compatible.

3.1.1.2 Progression of the effect

The **progression** of the adverse effect may be:

- **Suggestive,** when the adverse effect decreases or progresses in a typical way when the dose of the product is decreased or stopped, in the absence of any appropriate symptomatic treatment[3].
    - **Specific case of potentially fatal adverse effects** (such as anaphylactic shock, ventricular fibrillation or atrioventricular conduction disorders): the implementation of emergency treatment should not be considered as a reason for lowering the causality score of the case in question. The progression is then referred to as suggestive by default.
    - **Specific case of irreversible adverse effects** (including **death** when it is the direct result of the adverse effect reported); the reversibility of the reaction cannot be assessed. The progression is said to be suggestive. In this way, it remains possible to obtain an intrinsic score of 'very likely' (I4).
- **Non-suggestive,** when:
    - the adverse effect does not decrease, or decreases outside the expected time frame after discontinuation of the product, with or without appropriate symptomatic treatment , even though the symptoms are generally reversible;

3 The term 'treatment' refers to any decision leading to drug-based or non-drug-based treatment (including fasting).

- the adverse effect decreases significantly, without discontinuation of the production and without appropriate symptomatic treatment.

- **Impossible to interpret** for any other situation, including those where:
  - the adverse effect decreases after discontinuing the product and with appropriate treatment.
  - no information is available on the progression of the adverse effect and/or the discontinuation of product use.

3.1.1.3 Reintroduction of the product

Reintroduction refers to a resumption in the use of the suspected product[4] based on the same form of administration (oral or enteral)[5], when the adverse effect likely to be linked to the previous intake has disappeared. If the adverse effect is temporary and decreases within a few hours before the product is next taken, this last intake is considered as a reintroduction, even if it corresponds to the recommended consumption frequency. The reintroduction of a product is said to be:

- **R(+): positive,** if the same adverse effect reoccurs on reintroducing the product regardless of the dose (excepting cases of anaphylaxis, which are considered to be a positive reintroduction even if the clinical picture varies from one exposure to another);
- **R(-): negative,** if the adverse effect does not reoccur on reintroducing the product at an identical or higher dose;
- **R(0): absent** if the product has not been consumed again;

  or inconclusive, if the adverse effect did not reoccur after consumption was resumed at a smaller dose, or if no information is available concerning the recurrence of the reaction following the reintroduction of the product.

Specific case of congenital effects

When a pregnant woman consumes a product suspected of having an adverse effect on the foetus during her first pregnancy, the consumption of the same product during a second pregnancy will be considered as a reintroduction.

3.1.1.4 Establishing the chronological score

Information on the onset time, the progression of the reaction and the reintroduction of the product are combined to establish a chronological score ranging from C0 (zero) to C4 (high), as described in Table 1.

The occurrence of the adverse effect when a product is reintroduced is a key component in causal inference and therefore one of the main criteria. In this way, positive reintroduction (R+) of the product will raise the chronological score by one level. In contrast, negative reintroduction (R-) will lower the chronological score by one level, but only excludes the responsibility of a product in the occurrence of the adverse effect reported when the onset time is potentially compatible and the

[4] Same manufacturer, same composition on the label.

[5] Allergy tests such as prick tests or patch tests are not considered as reintroductions, even if conducted with the product suspected of causing the adverse effect when taken orally.

evolution is non-suggestive. If the product is not reintroduced (R0), the score obtained based on the time frame and the progression is maintained.

Table 1: **Establishing the chronological score**

	ONSET TIME OF THE ADVERSE EFFECT					
	Incompatible	Non-incompatible				
		Compatible		Potentially compatible		
PROGRESSION OF THE REACTION		***REINTRODUCTION***				
		R(+)	*R(0)*	*R(-)*	*R(+)*	*R(0)*	*R(-)*
Suggestive	C0	C4	C3	C2	C3	C2	C1
Cannot be interpreted		C3	C2	C1	C2	C1	C1
Non-suggestive		C2	C1	C1	C2	C1	C0

3.1.2 Aetiological score

The aetiological score depends solely on the information available on other causes that could potentially be responsible for the occurrence of the adverse effect. Calculated using Table 2, the aetiological score ranges from E0 (low) to E3 (high).

Three factors are taken into account:

- the **aetiological investigation**[6] conducted;
- the existence of one or more **factor(s) of risk or comorbidity**[7]**,** given that a product is more likely to cause an adverse effect when a factor of risk or comorbidity is present in an individual. If no aetiological investigation has been carried out, the aetiological score will be E2 rather than E1. In all other cases, the existence of a risk factor has no influence on the aetiological score;
- **possible interaction** with:
    - a **substance** (medication, alcohol, drug, etc.) **known to cause the adverse effect, and whose intake preceded** that of the product assessed without causing any adverse effect[8];
    - a **drug taken to treat a disease associated with the adverse effect,** whose efficiency may have been reduced by the product assessed, causing symptoms to reappear[9].

[6] Examinations seeking a positive diagnosis are excluded.

[7] For example: hypercholesterolemia and smoking are risk factors for strokes; Crohn's disease is a risk factor for abdominal pain; intense physical activity is a risk factor for rhabdomyolisis; etc.

[8] For example: a person taking paracetamol regularly with no adverse effects and who develops hepatotoxicity after taking a food supplement

In the same way as for risk factors and comorbidities, any suspected interaction will result in an aetiological score of E2 rather than E1 when no research has been conducted into other causes. In all other cases, a possible interaction has no influence on the aetiological score;

Table 2: **Aetiological score**

RESULT OF THE AETIOLOGICAL INVESTIGATION	
Another cause has been identified[10]	E0
No aetiological investigation conducted[11]	E1 (or E2)[12]
Incomplete aetiological investigation with frequent unexplored causes[13]	E2
Complete aetiological investigation: All frequent causes have been ruled out Or the product assessed has been formally implicated[14]	E3

Remark: the circumstances resulting in an aetiological score of E0 (e.g.: viral hepatitis confirmed biologically) do not allow us to formally rule out the co-responsibility of the product assessed (through specific hepatotoxicity, for example). The possible level of responsibility of the product assessed is taken into account in the final causality score through the chronological component.

3.1.3 Establishing the intrinsic causality score

The intrinsic causality score is the combined result of the chronological score and the aetiological score. Established using Table 3, it is used to determine the five levels of intrinsic causality:

I0: Excluded
I1: Unlikely
I2: Possible
I3: Likely
I4: Very likely

[9] For example: a person taking a well-balanced treatment for epilepsy and suffering a seizure following consumption of a food supplement

[10] For example: a confirmed infectious disease, a substance other than the product assessed (medication, alcohol, drug, etc.) known to result in the adverse effect (randomly or where intake began within a time frame compatible with the occurrence of the adverse effect)

[11] Including cases for which no aetiological investigation is justified (in particular, subjective or fugitive symptoms) and where the cause of adverse effects is assumed to be unknown

[12] In cases where no aetiological investigation is conducted (E1) but where one or more risk or comorbidity factors likely to have contributed to the adverse effect are identified, or interaction with a substance is suspected, the aetiological score is set at E2.

[13] Or for which details of examination results have not been reported

[14] For example: an adapted positive allergy test with the product assessed

Table 3: **Establishing the intrinsic causality score**

INTRINSIC SCORE	Aetiological score			
Chronological score	E0	E1	E2	E3
C0	I0			
C1	I1	I1	I1	I2
C2	I1	I2	I2	I3
C3	I2	I3	I3	I4
C4	I3	I3	I4	I4

3.2 Extrinsic causality score

The extrinsic causality score assesses the quality of the science demonstrating a causal relationship between an ingredient and an adverse effect. Established using Table 4, it is based on data from the literature at a given date.

Table 4: **Table establishing the extrinsic causality score of an adverse effect**

Well documented: Clinical or epidemiological study/studies Isolated clinical case(s) backed up by pathophysiological data	B2
Little documented: Isolated clinical case(s) not backed up by pathophysiological data Experimental studies on animals	B1
Non documented: No clinical cases and no clinical or animal studies[15]	B0

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety adopts the method of determining causality in nutrivigilance that was put forward by the Working Group on "Nutrivigilance" and validated by the Expert Committee on “Human Nutrition”.

This update to the method published in 2011 takes account of the changes submitted by the “Nutrivigilance” Working Group throughout its application and also of the remarks made following a test to establish concordance between assessors. This update mainly takes the form of:

[15] *in vitro* studies not taken into consideration

- further details on the conditions of implementation applicable to the method, with particular emphasis on the minimum information required to be able to apply the method, and the need for specialist medical expertise;
- a more discriminatory definition of the components involved in the intrinsic causality score with examples illustrating the different situations (aetiological investigation, risk factors, interactions) and a detailed description of specific cases (biological test results, adverse, irreversible or possibly fatal reactions, congenital effects);
- a new definition of score levels in extrinsic causality, taking account in particular of any existing pathophysiological data.

The causality method presented in this opinion provides the basis for a more discriminatory assessment of the relationship between the consumption of a product falling within the scope of nutrivigilance, and the occurrence of an adverse effect. It describes each component in the method in order to improve repeatability. At the same time, it underlines the need to take account of the risk of interactions with other substances consumed, particularly drugs.

This method of determining causality is systematically applied when analysing sufficiently well documented reports of adverse effects received by ANSES as part of the nutrivigilance scheme. For each report, a collective expert appraisal is conducted and validated by the “Nutrivigilance” Working Group.

Following this expert appraisal, ANSES informs the public authorities and manufacturers of the results of its analysis following reports. For the highest causality scores, the information is widely shared. Lastly, based on the reports and all the results, it sets priorities in terms of expertise appraisals assessing the health risks linked to the consumption of the products or ingredients implicated in these reports.

Dr Roger Genet

KEYWORDS

Effet indésirable, imputabilité, nutrivigilance, complément alimentaire.

Adverse effect, causality assessment, nutrivigilance, food supplement.

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ANNEX 1

Presentation of the participants

PREAMBLE: The expert members of the Expert Committees and Working Groups or designated rapporteurs are all appointed in a personal capacity, *intuitu personae*, and do not represent their parent organisation.

"NUTRIVIGILANCE" WORKING GROUP

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