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DE SÉCURITÉ SANITAIRE
DES ALIMENTS

Maisons-Alfort, 30 April 2009

OPINION

of the French Food Safety Agency regarding the risk to man of infection with the hepatitis E virus (HEV) after ingestion of *figatelli* (raw sausages containing pork liver)

THE DIRECTOR-GENERAL

Review of the request:

On 16 April 2009, the Directorate General for Food (DGAL) submitted a request to the French Food Safety Agency (AFSSA) for an opinion on the risk of human infection with the hepatitis E virus (HEV) after ingestion of *figatelli* (raw sausages containing pork liver).

Questions raised:

AFSSA was asked to give an opinion by 30 April 2009 on the following questions:

- Is the consumption of raw sausages containing pork liver (such as *figatelli* and Toulouse-style liver sausages) carrying the hepatitis E virus likely to cause a health risk to consumers?
- Would drying the produce be likely to reduce the health risk to consumers? If so, which drying protocol should be recommended?
- Would cooking the produce be likely to reduce the health risk to consumers? If so, what cooking protocol should be recommended?

In addition, AFSSA will be asked to give an opinion on the same questions concerning the consumption of meat from pigs, wild boar and deer.

Context of the request

The request made to AFSSA specifies the following contextual elements: *This request is in response to a declaration by Professor René Gerolami, Head of the Gastroenterology and Hepatology department at the* Hôpital de la Conception *in Marseille and by Dr Philippe Colson of the virology laboratory of* La Timone *(Marseille) revealing about twenty human cases of hepatitis E every year at the* Assistance Publique *hospital in Marseille (AP-HM). They showed that the factor that all these patients had in common was that they had eaten raw* figatelli*. They released this information on 10 April 2009 and it was widely taken up by the local and national media.*

The southern inter-regional epidemiology unit (CIRE) has written a summary of all human cases of which it was aware, which was sent with the request.

A sheet giving the composition of figatelli *and a table listing the ingredients of raw sausages taken from the industry code for the pork butchery, meat curing and preserving sector are included with this document.* Figatelli *are usually consumed raw, dried, cooked or barbecued. While waiting for AFSSA to issue its opinion, the DGAL asked the professionals concerned to establish upstream and downstream traceability and to apply a preventive embargo on the batches found to be positive and incriminated above.*

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Assessment method

Considering the short time allotted, an emergency collective expert assessment group (GECU) named 'Risk of human infection by the hepatitis E virus through ingestion of *figatelli*' was set up on 23 April 2009.

The Group has issued the following opinion in response to the first series of questions asked by the DGAL. A supplementary opinion on the other questions will be issued at a later date.

Discussion

1. Context and epidemiological situation

Context

The hepatitis E virus is known to be the main agent for acute hepatitis in countries with poor hygiene where it evolves in an endo-epidemic mode. In the industrialised countries, cases of hepatitis E were initially reported after a period spent in regions where it is endemic (7), especially among military personnel (13). Since 1997, however, autochthonous cases of hepatitis E in the United States in patients with no history of travel to endemic regions (36) have revealed the existence of a new process of infection for HEV and raised the question of their origin.

The discovery of natural infection with HEV in primates and pigs suggested exposure to the virus and the possibility of transmission between species (10). The hypothesis of a zoonotic origin for these autochthonous cases was raised as early as 1997 in the United States, when a variant known as Swine HEV was isolated and found to be genetically very close to human variants taken from autochthonous cases discovered during the same period and associated with genotype 3 (48). Since then, several variants of HEV have been isolated in both humans and animals, often with close genetic similarity which reinforces the hypothesis of zoonosis. Proof of a zoonotic component in HEV finally came with the observation in Japan in 2003 of about ten cases of transmission of the virus by the alimentary route from contaminated meat (40, 65).

Clinical description of hepatitis E in man

The incubation period for hepatitis E is between 3 and 8 weeks, with an average of 40 days (57). Approximately half the cases are asymptomatic or pauci-symptomatic. The prodromal phase of the disease is sometimes absent, sometimes short or can sometimes last for 2 weeks. The clinical picture is then similar to that for hepatitis A (21, 54, 57). The picture usually features asthenia, jaundice of the skin and mucous membranes and hepatomegaly. There may be other digestive clinical symptoms such as nausea, vomiting and abdominal pains. Some patients also suffer from hyperthermia, usually mild. The disease usually has a favourable outcome; recovery is usually spontaneous and without sequel, after 2 to 4 weeks. In 1 to 2% of cases, however, hepatitis E becomes complicated by acute liver failure (33) and can be life-threatening; liver grafting is often the only solution. Acute liver failure has been observed in patients with underlying liver disease (55, 59). Complications involving chronic liver conditions and cirrhosis have also been observed in immunosuppressed patients (20, 23, 29, 30). Hepatitis E therefore seems to be more serious than hepatitis A, with respective rates of mortality of 0.4-4% compared to 0.1-2% (53). It also appears that a higher incidence of acute liver failure due to HEV in pregnant women is reported in endemic regions, being as high as 20% during the third month of pregnancy. Several prospective studies, particularly those carried out in India, have investigated the relationship between hepatitis E and pregnancy (27, 31, 32, 35).

Epidemiological situation in France

General information

It should be emphasised that hepatitis E is not a notifiable disease in France. Surveillance of hepatitis E is performed by the National Reference Centre (CNR) for enteric transmission of enteric

hepatitis (hepatitis A and E) set up in 2002. The Virology Laboratories of the University teaching hospitals (CHUs) of Toulouse and Marseille make routine serological and molecular diagnoses of hepatitis E and collaborate with the CNR to synthesize the results.

Table 1 shows the number of cases of hepatitis E diagnosed by the HEV CNR, and distinguishes between imported cases (travel to an endemic region during the 3 months previous to onset of the disease), autochthonous cases and those with an unknown epidemiological context. It should be noted that in 25% of cases with an unknown epidemiological context, genotyping of the virus indicates genotype 3f, which is the genotype most commonly found in Europe.

Cases have been diagnosed in all regions of continental France and are found mostly in the south. Every year, more than half of the autochthonous cases have been recorded in the Midi-Pyrénées and PACA regions (9).

Since 2002, cases of autochthonous hepatitis E have increased. This may be the result of a real increase in the incidence of the pathology or an effect related to more reliable screening and/or diagnosis.

Indeed, there has also been a considerable increase in requests for analysis received by public and private laboratories, and health professionals, including gastro-enterologists, are paying it more attention (Table 1). In the Midi-Pyrénées region, where the effectiveness of diagnostic methods has been more or less constant because of the involvement of local clinicians and virologists, the number of cases has remained stable for the last 3 years, supporting the hypothesis that the epidemiological situation remains stable.

Table 1. Number of autochthonous cases of hepatitis E diagnosed in France between 2002 and 2008.

Year	2002	2003	2004	2005	2006	2007	2008
Number of patients tested	209	155	233	327	583	3500*	5500*
Certain cases							
- imported	4	11	4	19	14	14	23
- autochthonous	9	3	16	20	24	97	146
- epidemiological context unknown						5	49
Total	13	14	20	39	38	116	218

Description of 9 isolated autochthonous cases documented by the hepatitis E CNR, in 2008 and 2009, for which consumption of* figatelli *or liver sausages was reported:

Of the first 7 cases, 5 people were residents of the PACA region; 3 had travelled to Corsica in the 2 to 10 weeks before the onset of the symptoms and 4 others were unaware of any association with Corsica. They had all consumed pork liver sausages (2 cases) or *figatelli* (4 cases) or local Corsican pork products (1 case). Molecular characterisation of the viruses indicates that they belong to genotype 3f, the most frequently identified genotype in Europe.

Two other cases are currently being investigated:

In March 2009, a patient died of viremic acute hepatitis E. The viral genotype was characterised as type 3f. This patient had an underlying liver condition. It was found that the patient had consumed raw *figatelli* in the 2 to 10 weeks preceding the onset of the symptoms (end of December 2008). It was not possible to look for HEV markers in the *figatelli* as they had been consumed. This patient had been exposed to other potential risks of hepatitis E including the consumption of water from a private well (samples of water from the well are currently being analysed).

In March 2009 there was another autochthonous case involving a resident of Marseille who had consumed *figatelli* made using traditional methods in Corsica. The *figatelli* had been consumed during a meal shared by four people. The only diner at this meal to develop hepatitis E had eaten a small piece of raw *figatelli*. No other potential source of infection was identified.

Description of 2 episodes of outbreaks of hepatitis E with food origin that occurred in Southern France between 2007 and 2008:

In the summer of 2007, a familial outbreak which led to 3 autochthonous cases of hepatitis E (confirmed by PCR and sequenced as genotype 3f) in the Vaucluse *département* was investigated by the Southern CIRE. The 3 cases had shared a single meal (there were four diners) one month beforehand, during which *figatelli* had been served. The three diners who had consumed raw *figatelli* were diagnosed with hepatitis E. The fourth diner who had not consumed *figatelli* was not ill. No other common source of infection was identified.

In March 2009, the gastro-enterology and virology departments of the *Assistance Publique* service of the hospitals of Marseille reported a clinical case of hepatitis E diagnosed in September 2008 (positive PCR and sequencing as genotype 3f). This case was associated with 4 other pauci-symptomatic cases with seroconversion to HEV. All these patients had partaken of the same family meal at the beginning of August 2008 in Corsica. Of the 10 diners, all but one had consumed raw *figatelli*, the latter testing negative in PCR and seronegative.

2. Information on the hazard[1]

a. Identifying the hazard and the mode of transmission

Human HEV strains cannot be distinguished from animal strains

Four genotypes of HEV (types 1 to 4) can be distinguished in mammals, each genotype being divided into sub-types (24 sub-types).

Genotypes 1 and 2 are only found in humans, whereas genotypes 3 and 4 are found in both humans and animals. Some cases of hepatitis E appear to result from zoonosis.

Genotype 1 (5 sub-types, a to e) covers the human strains of HEV, responsible for epidemics and also for sporadic cases in African and Asian countries. Genotype 2 (2 sub-types, a and b) is found with limited distribution in Mexico and a few African countries (Chad and Nigeria). The strains of genotype 3 are mostly found in industrialised countries and may be either human or animal. At the time of writing, viruses of genotype 3 (10 sub-types, a to j) have only been identified in sporadic cases. Genotype 4 (7 sub-types, a to g) is found in humans and animals, mainly in South-East Asia.

Numerous swine strains of virus (genotypes 3 and 4) have been identified around the world. Phylogenetic analyses have systematically confirmed close genetic similarity between the human and animal strains suggesting that zoonotic transmission must take place (39).

In practice, based on compared sequences of isolates, and insofar as can be deduced by analysing genome fragments, it seems to be impossible to distinguish between human and animal strains, as intra-specific variability is at least as great as inter-specific variability. (2, 4, 24, 26, 52).

The human and animal strains of genotypes 3 and 4 can be transmitted between species.

The first experimental study of a possible crossing of the species barrier was carried out in 1998 (47). In this study, the Swine HEV strain, genotype 3, was transmitted intravenously to two rhesus monkeys and a chimpanzee which all developed viraemia and seroconversion. The human strain of genotype 3 (human US-2) was transmitted to specific-pathogen free (SPF) pigs. Similar studies were carried out for genotype 4: Arankalle *et al.* showed that inoculating rhesus monkeys with an Indian swine strain of genotype 4 led to viraemia and seroconversion in these animals (1). In 2008, in the United States, the team of Feagins *et al.* inoculated primates and swine with the human strain of genotype 4 TW6196E (17) which in both cases led to infection of the animals, with seroconversion, viraemia and faecal shedding of HEV.

[1] Part of the bibliographical review presented in this opinion is taken from a thesis by Fleuriane MARULIER, "*L'Hépatite E d'origine zoonotique*", a veterinary doctoral thesis, passed at the *Ecole Nationale Vétérinaire d'Alfort* in February 2009

There are documented cases of zoonotic transmission to humans through the consumption of infected meat:

At this time the literature includes two cases for which science has been able to prove the zoonotic origin of the infection and to compare the isolates. In both cases, the infection occurred in Japan.

The first case was described by Tei *et al.* in 2003 (65) and was related to the consumption of slices of raw meat from Sika deer. The meat had been frozen for preservation by the families, so it was possible to analyse it for HEV. The content of viral RNA was 10^5 copies/gram. Sequencing showed that isolates from the meat were 100% identical to those from the patients (genotype 3).

The second case was described by Li *et al.* in 2005 (40) in a woman aged 57 who had consumed a stew made from the meat of two wild boar that had been hunted. Ten people had consumed the meat but this woman was the only one to develop clinical hepatitis E. HEV was isolated in frozen pieces of meat from one of the two hunted animals. Phylogenetic analyses comparing ORF2 in the isolate taken from the patient with that from the meat, led to their being classified as genotype 3. Sequences were found to be 99.95% identical with only a single nucleotide being different out of the 1,980 of the ORF2.

In other cases, the origin of the infection was very probably food, but it was not possible to perform a comparative analysis of the isolates from the patients with those from the meat presumed to be the cause of the infection.

The first series of cases concerned 10 patients who had contracted acute or fulminant hepatitis E in Japan between 2001 and 2002 (70). Epidemiological analysis revealed that 9 of the 10 patients had frequently consumed pork liver, grilled but with different degrees of cooking, 2 to 8 weeks before onset of the symptoms.

In 2003, Matsuda *et al.* reported the case of two brothers hospitalised on the same day for the same symptoms of acute liver failure but in two different hospitals in Japan (45). Hepatitis E (genotype 4) was diagnosed for both patients retrospectively after the death of one of them. One of the risk factors was the regular consumption of raw wild boar liver during the 3 months preceding the onset of the illness. The two patients had been the only members of the family to consume wild boar liver and were the only ones to develop hepatitis E.

The following cases occurred in 2004 in Japan among 12 members of a local old folks association (62). After five clinical cases of hepatitis E had appeared among the members, it appeared that the only occasion when the 12 people had come together was a barbecue during which grilled wild boar was eaten. The phylogenetic analysis of the isolates of viral RNA found in two of the clinical cases showed homology of 99.4%.

The final case was reported by Masuda *et al.* in 2005, again in Japan (44). A 71-year-old man developed acute hepatitis E. About 60 days earlier, the man had consumed cheek of wild boar with his wife and his brother-in-law. Neither of the other two people showed any symptoms of hepatitis. Serological analysis on the brother-in-law, however, showed that he was highly seropositive for anti-HEV IgM and IgG, suggesting that he had recently suffered from a sub-clinical infection.

In the study by Tei (64), 89% of individuals who tested seropositive for anti-HEV antibodies had a history of having consumed raw venison, compared with only 46% of people who were seronegative, a significant difference (with $p = 0.035$). A German case study, directed by Wichmann in 2008, also found a significant correlation between infection with HEV and the consumption of wild boar meat (Odds Ratio 4.3; Confidence Interval 95 % [1.2-15.9]) and offal (OR 2.7; CI 95 % [1.2-6.2]) (66). Twenty percent of patients suffering from autochthonous hepatitis E reported consuming wild boar meat and 41% offal in the 2 months before the study compared with 6.7% and 18.5% respectively for control respondents.

We can therefore say that several studies have reported a link between the consumption of raw or insufficiently cooked pork, wild boar and venison and the onset of hepatitis E.

b. Carriage in swine and its prevalence in pork products (case of liver)

Carriage in swine - overview

Several species are capable of carrying the virus, but the main animal reservoir of HEV is pigs and the Suidae family more generally. Infection in domestic or farm pigs (*Sus scrofa domesticus*) is asymptomatic but the virus replicates and is shed widely. Many articles describe the isolation of viral RNA from this species on every continent (19, 25, 28, 37, 41, 42, 51, 58, 59, 63, 69, 71, 72). Other Suidae species are targets of HEV. For instance, several studies have isolated the virus in wild boar. In this species, HEV has been identified in Europe and Japan in the sub-species *Sus scrofa scrofa* (15, 30, 45) and *Sus scrofa leucomystax* (63, 64) respectively. In a more anecdotal vein, the study by Tanaka *et al.* in 2004 revealed the presence of the virus in miniature domestic pigs of Asian and American origin used for medical experiments (63). In all cases observed in Suidae, the HEV concerned was either genotype 3 or genotype 4.

Prevalence on pig farms

Many descriptive studies have been written on the hepatitis E virus in pigs in different countries but few have seriously investigated prevalence, i.e. including a sampling plan guaranteeing that the data are representative and that there are enough observations (farms, pigs etc.) to ensure sufficient precision in the estimates. Different studies use very different sampling units: prevalence may be estimated in animals (using an "average" pig, with pigs from different batches or farms), within farms or between farms. Different studies also collect very different types of information: seroprevalence (seeking IgG and sometimes IgM and/or IgA antibodies using serological techniques), prevalence of viral RNA (RT-PCR) in the serum, faeces (studies under farm conditions) or liver (purchasing of commercial pork liver).

With respect to serology, all the studies converge and reveal a very wide distribution of the virus on pig farms, if the criterion for 'positive' status is considered to be at least one seropositive pig per farm. Using this criterion, 15 out of 15 farms sampled were found to be positive in the USA in 1997 (48), 20/22 in New-Zealand in 2001 (19), 23/50 in Laos in 2007 (3), 10/10 in Mexico in 2005 (11) and 40/41 in Spain in 2008 (59). A retrospective study that looked at 208 farms sampled since 1985 shows that the virus could be considered as endemic throughout this period (204 seropositive farms out of the 208 analysed (8)).

At the level of individual pigs, at the age of six months, average seroprevalence is mostly lower, with very high variability in certain studies: 56% of pigs were found to be seropositive in Japan in 2005 (61), 23% in Argentina in 2006 (49), 81% in Brazil in 2005 (22) and 51% in Laos in 2007 (3). This high variability is the result of significant differences between the sizes of batches on given farms (4 to 58% for the Argentinean study (49) and 15 to 100% for the Brazilian study (22)). Breeding stock is also very frequently found to be seropositive (more than 60% (59)).

In continental France, a national survey currently under way suggests that seroprevalence is very high, with 90% of farms being positive and serological prevalence rates in animals varying from 2.5 to 80% on farms.

Influence of age

The presence of HEV in pigs varies in accordance with the animal's age (5, 46, 68). Before they are one month old, the animals present no viral RNA in their serum, probably because of protection against early-onset infection through maternal immunity. Viraemia starts to become detectable at the age of 2 months before peaking between 2 and 4 months (18, 59, 60). The prevalence of HEV RNA in the serum then gradually decreases before disappearing almost completely by 5-7 months, at the age when the pigs are slaughtered, depending on the farming practice. Concerning viral shedding, HEV RNA in faeces is first detected at about 2 months, with prevalence of shedding animals rising to a maximum between 2 and 4.5 months. Unlike the case with serum, however, the prevalence of animals shown by PCR to have positive faeces certainly diminishes with age but seems not to disappear entirely. According to these three studies, 8% of pigs being fattened or

ready for slaughter, i.e. between 5 and 7 months, in Taiwan and in England and up to 41% in Canada show viral shedding.

Dynamics of intra-farm infection

Under actual livestock farm conditions, the dynamics of infection by the hepatitis E virus are very similar to those described for most viral infections in pigs: acquisition of passive immunity from the sow *via* the colostrum (60% of piglets), progressive decline of passive antibodies until 10-12 weeks of age and seroconversion between 12 and 15 weeks of age corresponding to the peak of viraemia observed at 15 weeks (40% of animals (12)). In this study, the percentage of viraemic pigs increased from the age of 9 weeks to 15 weeks and then decreased gradually until slaughter. IgMs increased from 9 weeks of age and almost 100% of the pigs studied (n=16) were seropositive (IgG) at the age of 22 weeks. This dynamic, observed on a farm in Spain, also matches observations made in Japan where the peak of viral shedding via the faeces occurred between 1 and 3 months (75 to 100% of animals) before declining at 5-6 months (only 7% of animals) (50). The high seroprevalence towards the end of the fattening period shows that the virus is transmitted efficiently between animals of a given batch. This is confirmed by an experimental estimation of the base reproduction rate (R0) for the hepatitis E virus, judged to be 8.8, showing that it is theoretically possible for one infectious pig put in contact with a sensitive population to infect more than 8 animals while it remains infectious. The same study estimates that the length of the infectious period (aptitude for infecting a sensitive pig after contact) is 49 days (5).

Infection in pigs, target organs

The liver is the predominant target organ in pigs and the infection is clinically latent (38), although hepatitis lesions have been found in Spain in farm pigs during autopsies (identification of histological lesions) in a difficult sanitary context (Porcine post weaning multisystemic wasting syndrome) (43).

Studies of experimental infection show extra-hepatic distribution of the hepatitis E virus. After experimental intravenous infection, the virus may occasionally be found in the mesenteric and hepatic lymph nodes, the colon and the small intestine up to 20-27 days after inoculation (67). In this study, the virus was also found in the stomach and the spleen, though more rapidly (14 days after infection) and also occasionally in the kidneys, the tonsils, the saliva glands or the lungs. Only by inoculating pigs with a human strain was it possible to detect viral RNA in muscle up to 14 days after infection. A more recent study of pigs inoculated intravenously (IV) and of contact pigs shows that viral RNA can be detected by PCR in the longissimus, biceps femoris and iliopsoas muscles up to 27 days after inoculation in IV inoculated pigs and up to 27 to 31 days after the start of faecal shedding in contact pigs. The results of these studies rely on the amplification of viral RNA by qualitative PCR. No data exists on the quantification of the viral load in these different organs.

The presence of HEV in pork liver

It has been shown that HEV is found in food products containing pork. The first study of this type was carried out in Japan in 2003 on packaged pork livers sold in grocery stores on the island of Hokkaido (70). Analyses by RT-PCR showed that 2% of the livers tested contained viral RNA. Recently, there have been other studies on pork livers in the United States (15), India (34) and the Netherlands (6). The percentage of positive samples was 11.2 and 6.5% respectively.

In France, a search for the virus in pork livers at slaughterhouses has found viral RNA in about 3% of livers entering the human food chain (unpublished data communicated by the experts).

3. Information on raw sausage containing pork liver

Figatelli are composed of lean pork meat, pork fat, pork liver (a minimum of 30% imposed by the industry code for the pork butchery, meat curing and preserving sector), wine and various additives including salt (about 2.5%). The different ingredients are minced and then stuffed into a pork intestine. The *figatelli* are then heated at 25°C for 12 hours. After a 48-hour rest period they may be smoked (cold smoking, temperature < 30°C), and are then dried for 4 to 6 days (at about 14-16°C).

By the end of the process they have lost 12 to 15% of their initial weight. The pH is about 5 (4.8 to 5.2).

4. Answers to Request questions

a. Risk for consumers

Three populations are in particular danger of developing serious forms of hepatitis E:

- subjects with an underlying liver condition and the risk of acute liver failure (56)
- immuno-suppressed subjects at risk of chronic infection and cirrhosis (30).
- pregnant women (given the current state of knowledge, even though there are incomplete data on this subject concerning strains of genotypes 3 and 4) should be considered as being at risk of serious forms of infection.

The raw material for *figatelli* and related preparations is pork liver, an organ which is potentially very rich in viruses. (It should be emphasised that, as with all viruses, the hepatitis E virus cannot replicate in food matrices.) None of the phases in the production process is capable of inactivating HEV or eliminating it by partition. On the basis of a prevalence of 3% of livers containing the virus, mixing the pieces necessary to produce a batch considerably increases the risk of the final product being contaminated, even though it reduces the mean viral load[2]. Experience of viral security shows that the 'mixing' factor plays a key role in cases of transmission from biological products, which is not compensated for by dilution.
Two outbreaks in 2007 and 2008, one investigated by the CIRE Sud and the HEV CNR and the other by the CHU La Timone in Marseille, are very probably related to the consumption of *figatelli* (see above).
In March 2009, the AP-HM used PCR to test a batch of 7 *figatelli* purchased in a supermarket in Marseille, 5 of which tested positive in PCR with whole viral particles revealed by electronic microscopy. Sequencing identified two viral strains in the *figatelli* (genotypes 3c and 3f). These results (submitted for publication) support the presence of infectious viruses in the product: consequently, in the absence of any demonstrated or probable inactivation process, the presence of viral RNA must be considered to indicate the presence of infectious viruses. However, the viral load, which is a significant risk factor, remains unknown at this time, and the data concerning the frequency of contaminated batches need to be completed.

AFSSA's conclusion in response to the question "Is the consumption of raw sausages containing pork liver (such as *figatelli* and Toulouse-style liver sausages) carrying the hepatitis E virus likely to cause a health risk to consumers?"

The epidemiology of the infection in swine, the way in which liver sausages are prepared, the results of analyses of samples purchased from retail outlets, the existence of grouped and sporadic human cases whose probable or possible origin was the consumption of *figatelli*, all indicate that the consumption of this type of raw speciality presents a health risk for consumers. The consumption of this type of product causes significant exposure to the virus, even if the number of clinical cases remains low; the relative importance of the probable or possible factors of clinical expression is unknown (dose, specific mutations associated with tropism, factors of individual receptivity).

Because of the potential severity of the symptoms, AFSSA considers that such information should be communicated to consumers of these products. In addition, groups that are particularly susceptible to developing very serious forms of hepatitis E should receive information specifically adapted to the risk they run. These groups include subjects with an underlying liver condition with a risk of fulminant hepatitis, immunosuppressed subjects with a risk of chronic infection and cirrhosis, and pregnant women.

[2] For example, to produce a batch of about 2100 *figatelli* requires 75 livers. On the basis of 3% of livers being contaminated, the probability that the batch will be contaminated (i.e. will contain at least one contaminated liver) is $1-(0.97)^{75}$, or about 90%. The mean viral load of this batch will be 1.8 log lower than that of the initial liver.

b. The impact of drying

Drying is carried out at cold temperatures (below 30°C). The bibliography does not contain specific data on the effect of drying on HEV. This method of preservation must be considered to be ineffective for this type of virus.

AFSSA's conclusion in response to the question "Would drying the produce be likely to reduce the health risk to consumers? If so, what drying protocol should be recommended?"

AFFSA considers that, given our current knowledge, cold drying is not an effective technology for decontamination when HEV is present.

c. The impact of cooking

There are no permissive cells allowing HEV replication. Resistance to different treatments can therefore only be evaluated approximately, either by using knowledge of other viruses, or by relying on animal-based experiments.

Emerson et al. (14) therefore suggest that the hepatitis A virus (HAV) has greater thermo-resistance than HEV. As an example, the HAV virus, which is reputed to be among the most thermo-resistant, is eliminated after 5 minutes at a core temperature of 100°C.

If we consider only data concerning HEV, the work of Feagins et al. (16) has shown by bio-testing that the virus present in the liver could be infectious for swine but that viruses present by natural contamination are inactivated in diced pork liver (0.5 cm^2 to 1 cm^2) by achieving a core temperature of 71°C through either frying at 191°C for 5 minutes or cooking in boiling water for 5 minutes. On the other hand, incubation at 56°C for 1 hour was insufficient for total inactivation of the hepatitis E virus. These results are difficult to interpret, however, as the initial level of contamination was unknown.

AFSSA's conclusion in response to the question "Would cooking the produce be likely to reduce the health risk to consumers? If so, what cooking protocol should be recommended?"

AFSSA considers that cooking, if it is carried out at a sufficiently high temperature, is very probably an effective treatment for the hepatitis E virus. AFSSA considers that current data are insufficient to suggest practical methods for effective cooking.

These are AFSSA's conclusions in response to the first questions listed in the Request.

A supplementary analysis concerning the risks of contamination by the hepatitis E virus *via* the consumption of pork, wild boar or venison will be provided at a later date.

The Director General

Pascale BRIAND

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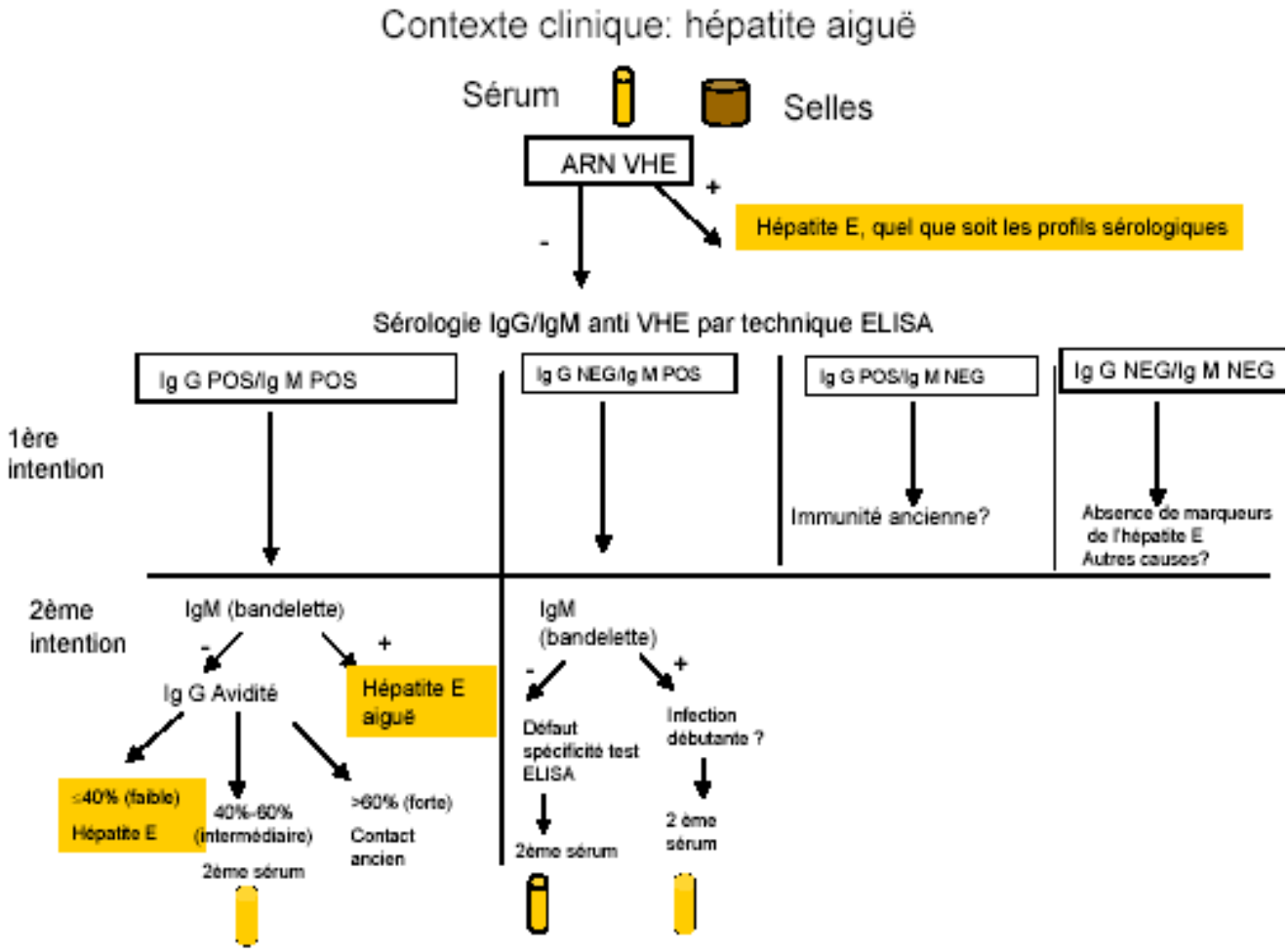
Keywords:

Figatelli, sausages, liver, hepatitis E virus, hepatitis E, risks, cooking, drying.

Annexe: algorithm for interpreting biological profiles for hepatitis E, 2007 (source: CNR)



Contexte Clinique: hépatite aiguë	Clinical context: acute hepatitis
Sérum	Serum
Selles	Faeces
ARN VHE	HEV RNA
Hépatite E, quel que soit les profils sérologiques	Hepatitis E, irrespective of the serological profiles
Sérologie IgG/IgM anti VHE par technique ELISA	Anti-HEV IgG/IgM serology using the ELISA technique
Ière intention	1st line
Immunité ancienne ?	Previous immunity?
Absence de marqueurs de l'hépatite E Autres causes ?	Absence of hepatitis E markers Other causes?
2ème intention	2nd intention
IgM (bandelette)	IgM (assay strip)
IgG Avidité	IgG avidity
Hépatite E aiguë	Acute hepatitis E
=<40% (faible) Hépatite E	=<40% (low) hepatitis E
40%-60% (Intermédiaire)	40%-60% (medium)
2ème sérum	2nd serum

> 60% (forte)	> 60 (high)
Contact ancien	Previous contact
Défaut spécificité test ELISA	Non-specific ELISA test
Infection débutante ?	Early stage of infection?
2ème sérum	2nd serum