Contamination of animal products: the minimum pathogen dose required to initiate infection

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Summary
When an animal product contains a low level of contamination (perhaps less than the minimum infective dose of a pathogen as determined experimentally), the theoretical probability remains that if a large number of animals are exposed to that product, at least one animal in the group will become infected. Such an infected animal could start an outbreak of the disease. These aspects, therefore, should be considered when risk assessments are performed. Foot and mouth disease virus in milk is used as an example.

Keywords

The virus concentration in a material is often expressed as ID_{50} (50% infective dose) per a certain weight or volume of the material, e.g. per gram or per ml. By definition, the ID_{50} is the dilution of material which would infect 50% of the individuals. To measure the ID_{50}, serial dilutions of the material are prepared and each dilution is inoculated into a number of susceptible animals or cell cultures. The dilution which theoretically would infect 50% of the inoculated hosts (or cell cultures) is calculated from the ratios of the number of infected hosts and the number of survivors or non-infected cultures for each dilution, according to the methods of Karber (2) or Reed and Muench (5). The main disadvantage of this method is the relatively small number of observations per dilution (particularly when rather costly animal test systems must be used) resulting in a large variation between test results (4, 7). Alternatively, the dilutions can be placed onto cell culture monolayers to determine the number of plaque forming units (PFU) contained in the original material. The dilutions which produce countable plaques (those which can be recognised as individual plaques) serve to calculate the number of PFU/ml or PFU/g. Although this method produces less variable results than the ID_{50} method, it is important to note that the same dilutions may produce different results with different cell systems. Usually, one ID_{50} requires several PFUs.

Sellers (6) reviewed the minimum infective dose (MID) of foot and mouth disease (FMD) virus required to infect susceptible animals of different species and by different routes of exposure. Some articles in this volume also make reference to the MID of different pathogens, and the reader may be left with the impression that a susceptible animal will not become infected when exposed to less of the pathogen than the MID. Such a concept would be in accordance with the generally accepted definition of the minimum threshold dose of a chemical contaminant or of the amount of radiation required to harm an individual (3), but it does not serve well for quantifying the risks of biological contamination.

Our fundamental assumption is that each infectious unit has a non-zero probability of independently infecting an animal, i.e. if one unit of a pathogen invades even one cell of a susceptible individual, the pathogen most likely multiplies or replicates in that cell. Its numerous offspring are likely to invade other cells, leading to disease or death.

Therefore, for FMD virus (FMDV) contained in an animal product such as meat or milk, to be ‘infectious’, a virus unit must be in the right place at the right time. Higher concentrations of virus obviously have a better chance of adhering to and invading a susceptible cell, but the exposure of many cells to low virus concentrations also may lead to infection of at least one of the cells. FMDV usually is able to invade and replicate in epithelial cells of the tongue, when placed there by intradermal (IDL) tongue inoculation, but the same amount of virus may only occasionally come into contact with a susceptible cell when administered by a different route. Thus the feeding of contaminated material is about 4-5 orders of magnitude less efficient at starting ‘infection’ than the IDL inoculation (6).
The probability that a contaminated product infects at least one animal from a group of susceptible hosts is a function of the level of contamination of the product, the probability of contamination of the hosts and the number of animal hosts exposed, and can be modelled as a binomial process.

For example, imagine that 100,000 PFU have a 50% probability of starting an infection if this amount of FMDV is fed to a pig. If this occurred, it would mean that at least one PFU was able to invade and infect a cell. Assuming that each virus particle in a dose has the same probability $p$ of invading and infecting a cell, then:

$$0.5 = 1 - (1 - p)^{100,000}$$

which gives $p = 6.93 \times 10^{-6}$.

Thus, one PFU has a probability of $6.93 \times 10^{-6}$ of infecting a pig. In the paper by Donaldson (1) in this issue, processed milk from an infected premises could have an FMDV titre of $10^{1.9} - 10^{2.9} \text{ID}_{50}$ per litre, approximately 500 PFU/litre.

The question 'What is the probability that at least one pig becomes infected when, for example, each of 100 pigs is fed one litre of this milk?' can now be examined.

The probability of this occurrence can be modelled by the same binomial process equation:

$$P = 1 - (1 - q)^n$$

where:

$P$ is the probability of infection of at least one pig

$q$ is the probability that the PFU in a litre of milk will start an infection in a pig

$n$ is the number of pigs;

$q$ is given by the equation: $q = 1 - (1 - p)^{500}$

where:

$p$ = probability of an individual virus particle infecting a pig (as stated above)

$q = 1 - (1 - 6.93 \times 10^{-6})^{500} = 0.00346.$

Thus

$$P = 1 - (1 - 0.00346)^{100}$$

which gives

$P = 0.293.$

Feeding each of 100 pigs with one litre of this milk thus results in a probability of 29.3% that at least one pig gets infected. If a litre of this milk were fed to each of only 20 pigs, there would still be a 6.7% probability that at least one pig contracts FMD. In other words, when sufficient numbers of susceptible animals are exposed to products which have low levels of contamination (and even if all individual animals receive less than the so-called MID) there is still a chance of infecting one animal from the group. For a highly contagious disease such as FMD, this means spread to susceptible contact animals and the likelihood of starting an epidemic.

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**Contamination des produits d'origine animale : la dose pathogène minimale requise pour déclencher une infection**

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**Résumé**

Lorsqu'un produit d'origine animale présente un faible niveau de contamination (peut-être inférieur à la dose infectante minimale d'un agent pathogène, telle que déterminée expérimentalement), il reste la probabilité théorique que, si un grand nombre d'animaux sont exposés à ce produit, au moins un animal soit infecté sur l'ensemble du groupe. L'animal ainsi infecté peut être à l'origine d'un foyer de maladie. Cela doit donc être pris en considération lors de toute évaluation des risques. Les auteurs illustrent leur analyse par le cas du virus de la fièvre aphteuse dans le lait.

**Mots-clés**

Analyse des risques - Dose infectante minimale - Dose minimale efficace - Fièvre aphteuse.
Contaminación de productos de origen animal: la dosis patogénica mínima requerida para que se inicie la infección

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Resumen
Cuando un producto de origen animal contiene un nivel bajo de contaminación (inferior, digamos, a la dosis infecciosa mínima de un patógeno determinada experimentalmente), subsiste la posibilidad teórica de que, suponiendo que un gran número de animales se expusieran a dicho producto, por lo menos uno de ellos resultara infectado. Ese animal infectado podría dar origen a un brote infeccioso de la enfermedad. Es necesario, por consiguiente, tener en cuenta este aspecto de la cuestión cuando se realizan evaluaciones de riesgos. A título de ejemplo se considera el caso de la contaminación de la leche por el virus de la fiebre aftosa.

Palabras clave

References