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Welzijn en Sport*

Bijlage 12
Dose-response for inhalation

Appendix to RIVM Report 2017-0062
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1 Dose-response for inhalationIntroductie OPS

1.1 Introduction

In this document we describe how to make the step from exposure, as calculated by the modified OPS simulation (see the main VGO document), to illness. The step from exposure to illness is made by applying a dose-response model, which gives the probability of illness as a function of exposure dose. There are several issues when applying this paradigm to our situation of continuous application to low doses of inhaled organisms.

Firstly, dose-response relations for enteric micro-organisms are developed for ingestion. We have found no literature references for inhalation, for our main micro-organisms: E. coli, Campylobacter and Staphylococcus. Note that for micro-organisms that are well known to be harmfull following inhalation, dose response relations are known. For example, for Q fever, B. anthracis or Legionella., or viruses such as the Coxsackievirus (Haas, 1999). It is believed that respiratory infection due to enteric pathogens is mainly due to swallowing the ingested organisms (Pillai, 2007). Hence, we will also follow the route via ingestion, in the absence of inhalation models and data. In the literature, the fraction of ingested organisms is not agreed on, rangeing from 10% (Medema, 2004) to 50% (Brooks, 2005). However, those estimates are poorly founded in theory or data.

In order to quantify the amount of inhalation and ingestion, based on characteristics of the human subject (inhalation rate, volume, mount/nose breathing), and of the pathogen (size-distribution of aerosols, virulence), a dose response relation should be based on dosimetric principles. The most complete dosimetric model is that of the ICRP (Bailey, 2007, ICRP). The appendix to this document describes in more detail the ICRP model which we use to translate a dose to an ingested amount of organisms. It is a compartemental model, idealising the human alveolar tract (Hofmann, 2011). To give an indication, according to the ICRP model, for an adult male at light exercise, 23% percent of inhaled aerosols of mean diameter of 1 micrometer ends up in the upper airways (ET2 region). Such an individual inhales 1.5 m^3/h air.

Secondly, it is not evident how a received dose should be interpreted. In the case of ingested enteric micro-organisms the dose is usually set by considering a meal with an accompanying portion size and bacterial concentration to derive an instantaneous dose. The dynamics of infection are on a much shorter timescale than the time between meals, which justifies this assumption. However, in the case of inhalation, the exposure is continuous, and discrete dosing events are hard to define. There has been some work in recent literature on time-dose-response models, taking into account the continuous nature of exposure (Huang, 2009) . We will see however, that the concentration to which a subject is typically exposed is so low, that the dose may be considered very low

(in the order of one organism), and separated by sufficient time to consider them discrete doses.

A third consideration is the impact of immunity. Most dose-response models that are currently applied do not take into account the beneficial effect of boosting of the immunse system by repeated exposure to low doses of a pathogen. However, it has been shown for Campylobacter, that the impact of immunity may be substantial (Havelaar, 2014). Moreover, in our situation we are exactly in the regime where immunity matters: low doses and frequent exposure. We will pay some attention to this issue in our scenario analysis. Due to the large uncertainties in the impact of immunity those analyses will have to be exploratory.

1.2 Exposure assessment

As our model organism we choose Campylobacter, since it is the only pathogenic micro-organism measured in the vincinity of farms. However, only DNA was measured using the PCR technique, and no culturing was performed. Hence, we have no information on the amount of viable organism. For this reason, as a substitute we use the number of living E. coli micro-organisms. It is thought that E. coli may be more resistant than Campylobacter. However, although there are some indications, there is no data to quantify this effect. We have to acknowledge though, that this will bias our results towards higher incidence.
A second reason for choosing Camplylobacter is the availability of dose-response relations, and some knowledge of the impact of immunity. Finally, there is indirect evidence for a significant contribution of Campylobacter infections via an environmental route in the neighbourhood of poultry holdings. This is further elaborated on in the discussion.

For our scenario we picture individuals located at 100m downwind from a poultry farm. Taking as a E. coli organisms, we have on average 3% positive samples, with 1.5 organism per m^3 positive sample (see main VGO report, Figure 4.1). Hence multiplying a typical breathing rate of 1.5 [m^3/hour] for a male in light exercise (ICRP, 1994), with the number of organisms per cubic meter gives 2.25 organisms per hour, when E. coli are present (3% of the times).

According to the ICRP model for a male subject in light exercise, 23% of the inhaled matter is deposited in the upper airways (Valantin, 2002). From the model presented in (ICRP, 1994) we can derive an equation describing transport from the ET2 (nasal region) to the gastro-intestinal tract (i.e., swallowing),

$$GI(t) = D(1 - \exp(-\lambda t))$$

where D is the inhaled dose, and λ=100 per day. As an illustration, after one hour, this model predicts that 98% percent of the deposited matter is swallowed. After 10 minutes, 50% of the dose is swallowed. In one minute, 7 percent of the dose is swallowed. Given the much lower clearance rates from ET2 to other compartments, we will assume that all organisms are swallowed.

Hence, of the 2.25 organisms per hour, 23% is swallowed, this equals 0.52 organisms. This, we interpret that once every 2 hours a single organism is swallowed. Also including the 3% positive samples yields a single Campylobacter every 67 hours.

1.3 Probability of infection

The probability of infection given ingestion of a single Campylobacter organism is estimated at 0.686 (Teunis, 2005), implying a 68.8% chance of infection every 67 hours. Put another way, there is a probability of 1/67 of encountering a Campylobacter each hour, and a 68.8% probability of infection, giving a 1% probability of infection each hour.

1.4 Probability of illness

The probability of illness is more problematic, since different models are used in practice. The most prevalent model assumes a probability of 3% for illness given infection (Havelaar, 2000), ignoring dose dependency. In our case, in the presence of extremely low doses, we consider this unrealistic.
Teunis et al., (Teunis, 2005) propose a dose dependent model given by

$$P(illness\,|infection) = 1 - (1 + \eta D)^{-\rho}$$

with $\eta = 1.23 * 10^{6}$ and $\rho = 8.13 * 10^{-7}$ yielding at dose D=1,

$$P(illness\,|infection) = 1.14 \times 10^{-5}$$

Combining this with our estimate of 1% probability of infection per hour yields a probability of illness of 1x10-7 per hour.

1.5 Effect of immunity

In our scenario, we are in the regime of repeated exposure to low doses, which may induce protective immunity, lowering the overall risk. Little is known of the effects of acquired immunity, since reliable data to quantify the effects is scarce. Nonetheless in (Havelaar, 2014) an estimate is made of the impact, depending on dose and frequency. From Figure 1 in this article we find an inflation factor of about 10%, which indicates that the probability of illness in the presence of acquired immunity is a factor ten lower as compared to the calculation in the previous section.
It is thought provoking that the frequent exposure to low doses via the airborne route may actually be protective. At the current level of scientific knowledge, and in the presence of considerable uncertainties, we are not in the position to prove or disprove this hypothesis yet.

1.6 Risk assessment

To assess the magnitude of the number " a probability of illness of 1x10-^{7} per hour ", consider working eight hours a day, for 250 days a year. The probability of at least one illness event is

$$1 - (1 - 1 \times 10^{-7})^{8*250} = 2 \times 10^{-4}$$

Hence, considering 100.000 individuals, we obtain 20 illness cases.

Estimates for the Netherlands are about 100.000 per 17 million inhabitants per year, i.e. 588 per 100.000 inhabitants. Thus in this scenario about 1 in 30 Campylobacter cases is attributable to inhalation. In the presence of immunity, the probability of illness would be about 10% lower, and about 1 in 300 Campylobacter cases would be attributable to the airborne route.

1.7 Discussion

The quoted numbers of illness cases should be interpreted with care since,

- Working 8 hours a day for 250 days at 100m from a farm is an extreme scenario, meant to illustrate hazards in a risky setting
- The exposure estimate is calculated for the centre of the plume, where concentrations are highest, further away from the plume, concentrations of Campylobacter in the air will be significantly lower.
- The actual inactivation rate of Campylobacter in the air is unknown

However, the scenario is not entirely without merit, considering the following points

- We considered only average exposure, while exposure during peak events can be much higher
- We took data from the measurement days. There will be days in the year with more favourable transmission characteristics (stable atmosphere, high wind speed), when exposure will be elevated
- For subpopulations with enhanced susceptibility (the elderly, immunocompromised), the risk could be higher.

At the very least, the current work shows that infection and illness via the airborne route, in the vicinity of poultry farms is certainly a possibility. Also note that we consider only infection by Campylobacter here, in reality the airborne route will be relevant for a wider range of pathogens.

As an alternative scenario, somewhat more extreme we may consider the background concentration of E.coli, 100 organisms, dead and alive per cubic meter (VGO main report, Fig 4.1). The difference between dead and alive organisms is about a factor 10.000, which yields 10^{-2} viable organisms per cubic meter. Compared to the 1.5 organisms at 100m, this is a reduction of a factor 150. Since we are in the low-dose regime where oure calculations are to good approximation linear, this more realistic scenario (but also more uncertain due to the extrapolations) yields 0.13 illness cases per 100.000 inhabitants. One in 4500 cases would be attributable to the airborne route. Again, this alternative scenario is only indicative, due to great uncertainty. Nonetheless, it gives an indication that airborne transmission is a realistic possibility, not only directly in the neighbourhood of the farm.

There are more indications in the literature sugesting that Campylobacter may cause illness via an environmental pathway. In (Friesema, 2012) the authors show that in 2003, after large scale culling

due to an outbreak of avian influenza, the incidence of campylobacterios declined most in the vicinity of culled farms. This is a strong indication that a non-alimentary route is responsible for part of the disease incidence. Consumption of poultry meat also declined during the outbreak, however, not specifically in the culling area but rather nationwide.

2 References

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3 Appendix, Using the ICRP model for dose determination

3.1 Human Parameters

As a first step we need reference values for individuals in the target area, stratified by age, sex, and activity. The values needed are,

- V_T, the tidal volume [mL], the amount of air breathed in one inhalation
- $\dot{V}$, the flow rate [mL/s], the rate of air flowing per second
- f_R, the respiration frequency [min-1], the number of breaths per minute
- SF, scaling factor for width of airways

Table I lists the values as recommended by ICRP.

		Female			**Male**		
Activity	**Age**	**Frequency**	**Volume**	**Flow**	**Frequency**	**Volume**	**Flow**
heavy	10	46	667	1128	44	841	1128
	15	38	1127	1428	36	1352	1622
	adult	33	1364	1500	26	1920	1670
light	1	46	127	194	46	127	194
	10	32	583	622	32	583	622
	15	24	903	722	23	1000	767
	5	39	244	317	39	244	317
	adult	21	992	694	20	1250	833
resting	1	34	74	83	34	74	83
	10	17	304	172	17	304	172
	15	14	417	194	14	500	233
	5	23	174	133	23	174	133
	adult	12	444	178	12	625	250
sitting	1	36	102	122	36	102	122
	10	19	333	211	19	333	211
	15	16	417	222	15	533	267
	5	25	213	178	25	213	178
	adult	14	464	217	12	750	300

Table I. Recommended

Table II. Recommended values for the scaling factor (SF)

	Female	**Male**
Age	**SF**	
1	2.20	2.20
10	1.26	1.26
15	1.09	1.04
5	1.55	1.55
adult	1.08	1.00

Table III Fraction of total ventilatory airflow passing through the nose, Fn, in nasal augmenters (normal nose breathers) and in mouth breathers.

Level of exertion	Nasal augmenter	Mouth breather
Sleep	1.0	0.7
Rest	1.0	0.7
Light exercise	1.0	0.4
Heavy exercise	0.5	0.3

3.2 Deposition and clearance

Our focus is pathogens that get inhaled and subsequently swallowed, hereby ending up in the gastro-intestinal (GI) tract, where the usual dose-response relations may be employed. This amounts to calculating firstly the deposition in the extrathoracic (ET) region (see Figure 1), and subsequently clearance via the GI tract.

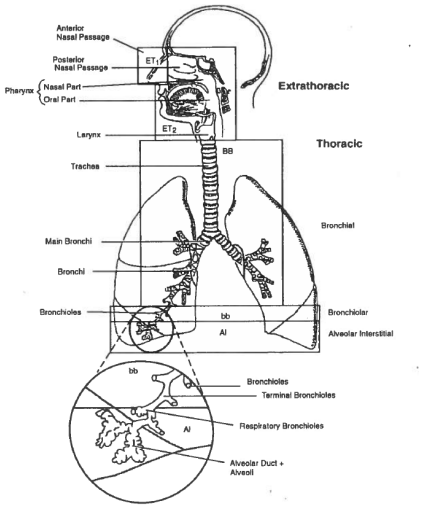

Figure 1. Summary of anatomical regions in the respiratory tract.

For deposition, the anatomical regions are viewed as a series of filters in sequence (Figure 2).

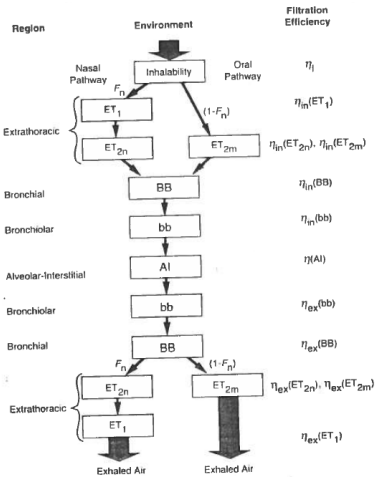

Figure 2. Schematic representation of the filters of the respiratory tract, during an inhalation-exhalation cycle.

On inhalation, the fraction of the air that reaches filter *j* is given by

$$\phi_j = \begin{cases} 1 & \text{if } j = 0 \qquad [environment] \\ 1 - \frac{1}{V_T}\sum_{k=0}^{j-1} v_k & \text{if } 1 \le j \le (N+1)/2 \qquad [inhalation] \\ \phi_{N-j+1} & \text{if } \frac{N+1}{2} < j \le N \qquad [exhalation] \end{cases}$$

Here, N is the number of filters (*N=7* for the oral pathway, *N=9* for the nasal pathway), V_T is the tidal volume, and v_k is the volume of filter *k*. Let I_j be the number of particles arriving at filter *j*, where I_0 indicates the number of particles in the environment. The fraction F_n of tidal flow passing through the nasal passage (see Figure 2) given in Table III. The filtration efficiency is defined as

$$\eta_j = 1 - \frac{I_{j+1}}{I_j}$$

Combining the fractions of air with the filtration efficiency, we calculate the number of particles deposited at filter *j* as

$$D_j = \eta_j \phi_j \prod_{k=0}^{j-1} (1 - \eta_k)$$

A little algebra shows that this formula can also be described recursively as

$$D_1 = \eta_1(1 - \eta_0) = \eta_1^2$$
$$D_j = D_{j-1}\eta_j \frac{\phi_j}{\phi_{j-1}} \frac{1 - \eta_{j-1}}{\eta_{j-1}}$$

where $\eta_1 = 1 - \eta_0$ is an imaginary pre-filter also known as 'inhalability'. This inhalability is modelled as

η _1=0.5[1+e^(-0.06d)]

where *d* is the aerodynamic diameter.

Now, clearance to the GI tract is only possible from the ET_2 region. Therefore we concentrate on deposition from this region only. From Table 12 of [ICRP 1996] we find for nose breathing the following expressions for aerodynamic and thermodynamic deposition efficiencies.

$$\eta_{ae} = 1 - \frac{1}{1 - 5.5 \times 10^{-5}\left[d^2 \dot{V}_n SF_1^3\right]^{1.17}}$$

$$\eta_{th} = 1 - e^{-15.1\left[D(\dot{V}_n SF_1)^{-\frac{1}{4}}\right]^{0.538}}$$
$$\eta_2 = \sqrt{\eta_{ae}^2 + \eta_{th}^2}$$

Here, $\dot{V}_n$ in [cm^3 /s] is the volumetric flow rate through the nose, given by the flow rate (Table I) multiplied by the factor for nose Fn for nose breathing. For any reasonable value for D, around 10-^{4} to 10-^{7}, (see Seinfeld en Pandis (2006)) we find that η_{th} can be safely neglected. Hence, the total deposition becomes

$$\eta_2 = 1 - \frac{1}{1 - 5.5 \times 10^{-5}\left[d^2 \dot{V}_n S F_1^3\right]^{1.17}}$$

The intake I_0 is calculated from the concentration of organisms *C* [organisms/m^3], the breathing rate *B* [m^3/h] and exposure time *t* [h]:

$$I_0 = CBt$$