What Do We Know About The Health Risks Of Nitrate In Drinking Water?

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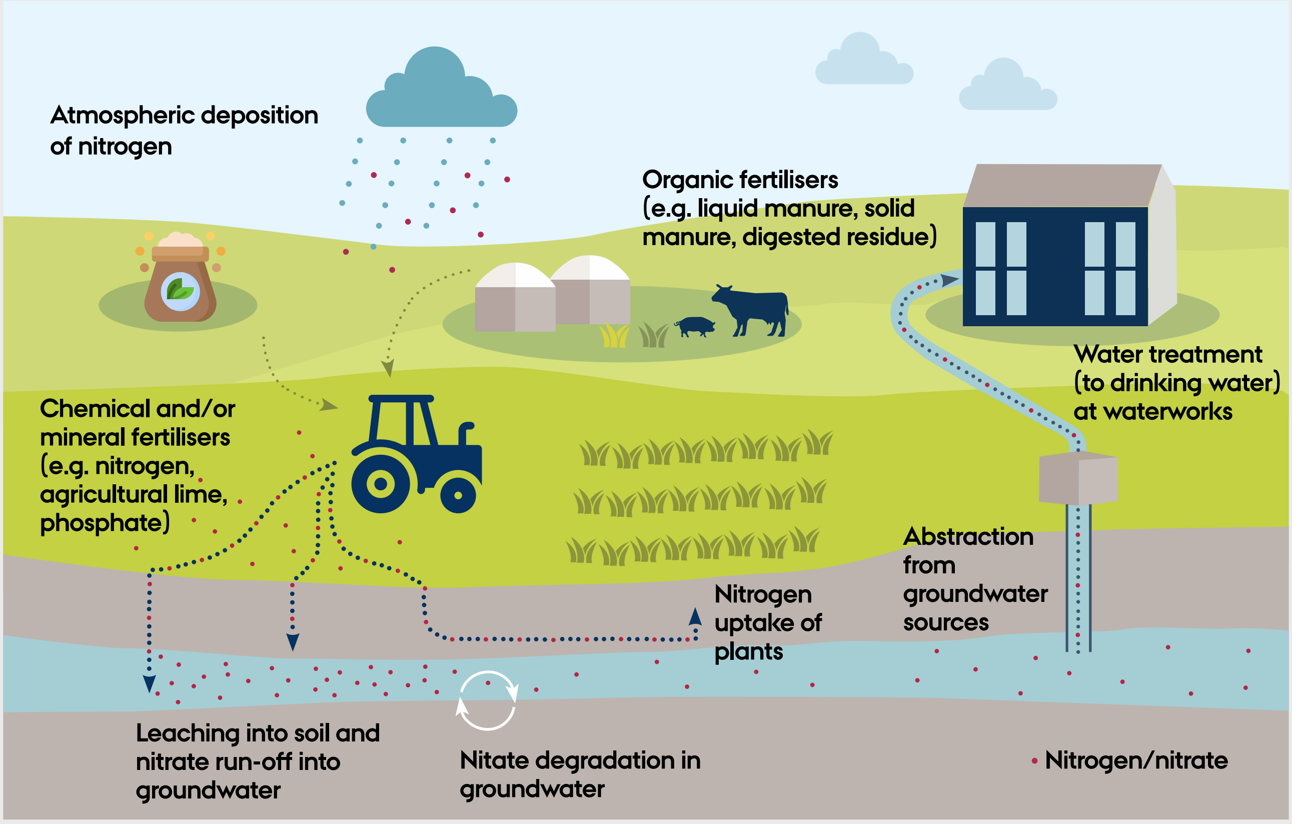
Photo: elenacreativaea

Nitrate is a common drinking water pollutant worldwide, typically due to **leaching of nitrogen fertilizers from agriculture**. In addition to negative consequences on surface water ecosystems, contaminated surface- or groundwater can reach people through drinking water. In particular, shallow groundwater wells can have very high nitrate levels if the groundwater sources are not sufficiently protected. This affects private well users, but also public supplies in areas where the geological conditions do not allow groundwater sourcing from deeper, nitrate-free aquifers. In Europe, drinking water should not exceed a maximum threshold of 50 mg nitrate per liter, according to the European Union (EU) Drinking Water Directive.

Figure 1. Agriculture and drinking water

Agricultural activity can result in the leaking of nitrate into groundwater, which is later sourced, treated and distributed as drinking water.



Source: Deutsche Verein des Gas- und Wasserfaches e.V. (DVGW) https://www.dvgw.de/english-pages/topics/water/nitrates-and-drinking-water)

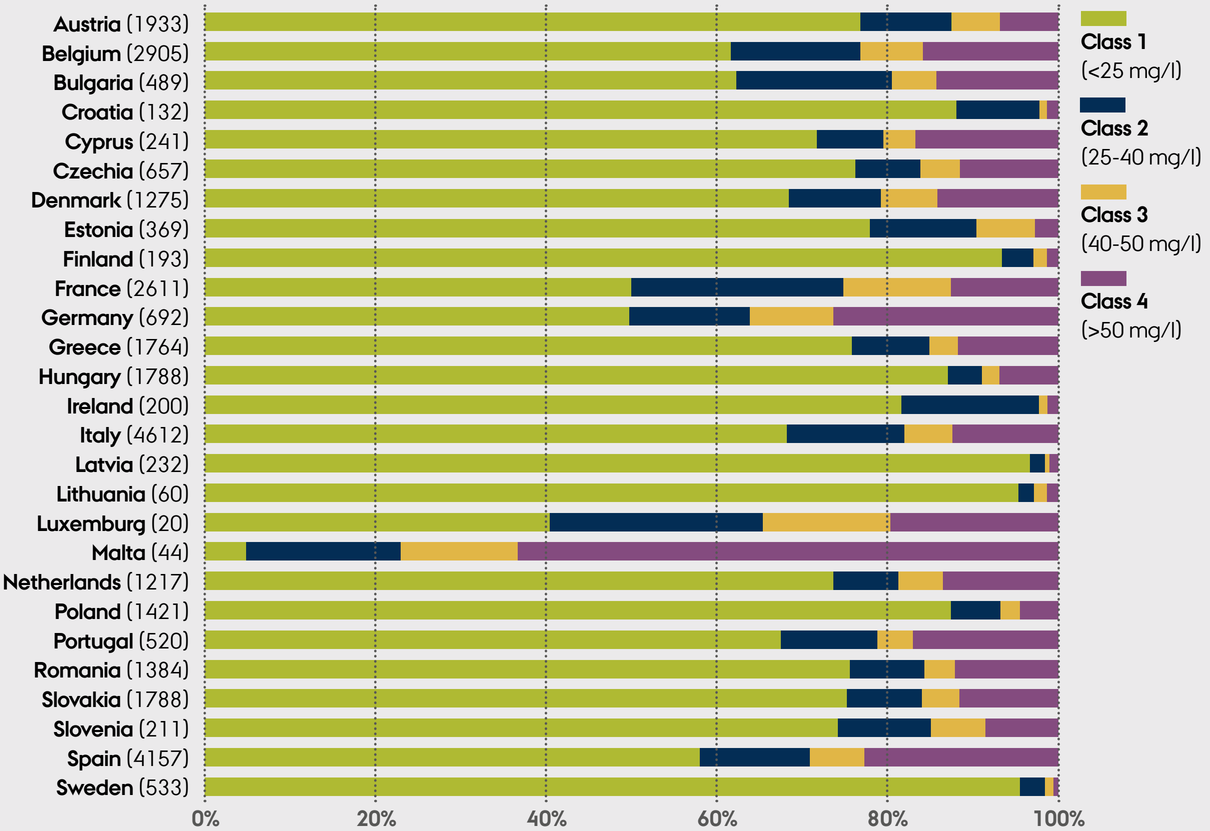
Box 1. What happens when we ingest nitrate from our drinking water?

When nitrate is ingested, the body converts it into **nitrite**, which can bind to hemoglobin in the blood and reduce its ability to transport oxygen. This leads to oxygen deprivation in tissues and organs - and can trigger a condition in infants known as '**blue baby syndrome**' (the medical term is *methemoglobinemia*). To protect babies, the maximum concentration in the European Union (EU) is 50 mg nitrate per liter. There is robust evidence and scientific consensus on the causal relation between excessive nitrate exposure and methemoglobinemia. Recent epidemiological studies also indicate a correlation between nitrate in drinking water and a higher frequency of low birth weight, birth defects, preterm delivery and childhood cancer. However, additional evidence is needed since there are not enough studies and there are frequent data gaps on water consumption patterns, nitrate intake from diet, and the intake of nitrosatable drugs.

Nitrate exposure may also negatively affect adult health. Nitrate can convert into *N*-nitroso-compounds in the body, which, according to experimental studies in animals, are known to have carcinogenic effects for the digestive system. Several epidemiological studies suggest that **cancer risk** increases at levels well below 50 mg nitrate per liter.

Figure 2. Nitrate levels in groundwater during 2016-2019 (based on Member State reporting according to the Nitrates Directive)

In the EU, all countries report groundwaters with concentrations above the maximum allowable concentration (50 mg/L), with substantial variation (see figure), which shows that nitrate pollution of groundwater is a prevalent problem in most EU countries.



Source: European Environment Agency.
https://www.eea.europa.eu/en/analysis/indicators/nitrate-in-groundwater-8th-eap

How Do Scientists Establish the Associations between Exposures to Drinking Water Nitrate Pollution and Health Risks?

Exposure-response functions are essential for environmental and socio-economic analyses since they allow us to estimate how much the risk of a disease or premature death can be expected to increase statistically for a given increase of pollution.

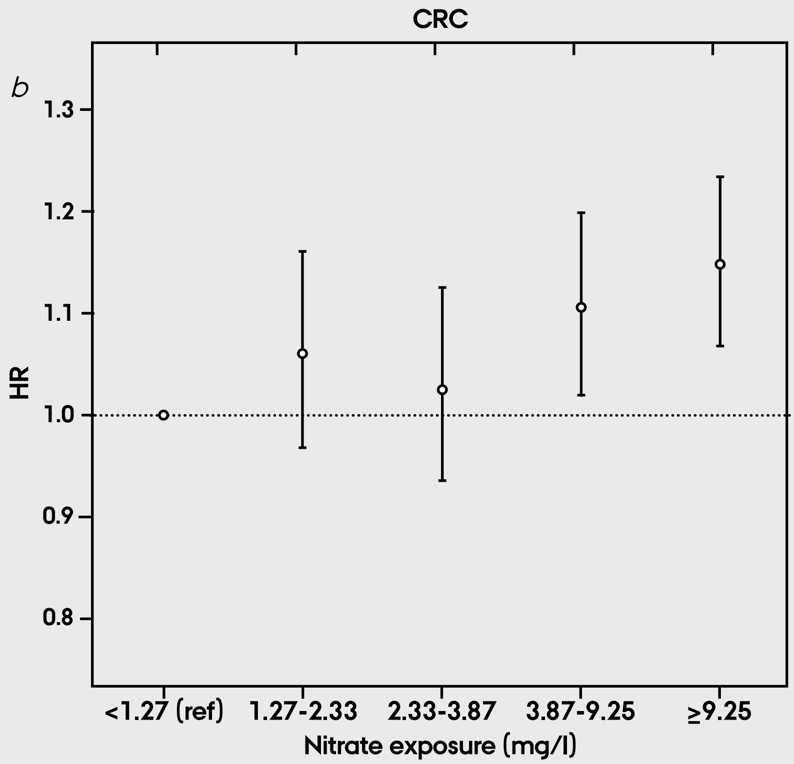
An exposure-response function is a mathematical relationship that describes how the risk or severity of a health outcome changes with different levels of exposure to a particular environmental factor. Therefore, this function is a **key tool** in environmental health studies as it quantifies the link between the level of exposure (e.g., to nitrate in drinking water) and the probability of a health effect (e.g., cancer, premature birth).

The x-axis of the function shows the exposure level, which is represented by the concentration or dose of the environmental factor. The y-axis of the function indicates the response (in this case the health outcome colorectal cancer) which can be measured as the incidence rate or the **relative risk** of the adverse effect, which refers to the risk of a health outcome in one group exposed to the environmental factor compared to the risk of the same health outcome in a group that is not exposed or exposed to the lowest levels.

An exposure-response function describes the relationship between **the concentration of drinking water nitrate and the incidence of colorectal cancer**, for example. If the exposure-response function is linear, it indicates that for each given increase in drinking water nitrate, there will be a corresponding increase in the risks of colorectal cancer in the population.

Figure 3. Exposure-response function between nitrate exposure and risk of colorectal cancer

If the risk is above 1, there is an increased risk of colorectal cancer in the exposure category when compared to the reference category. The lines and whiskers indicate the 95% confidence intervals: if they do not cross the dotted line (HR=1), we call the association statistically significant.



Source: Schullehner J, Hansen B, Thygesen M, et al. Nitrate in drinking water and colorectal cancer risk: A nationwide population-based cohort study. Cancer Epidemiology (2018). https://doi.org/10.1002/ijc.31306

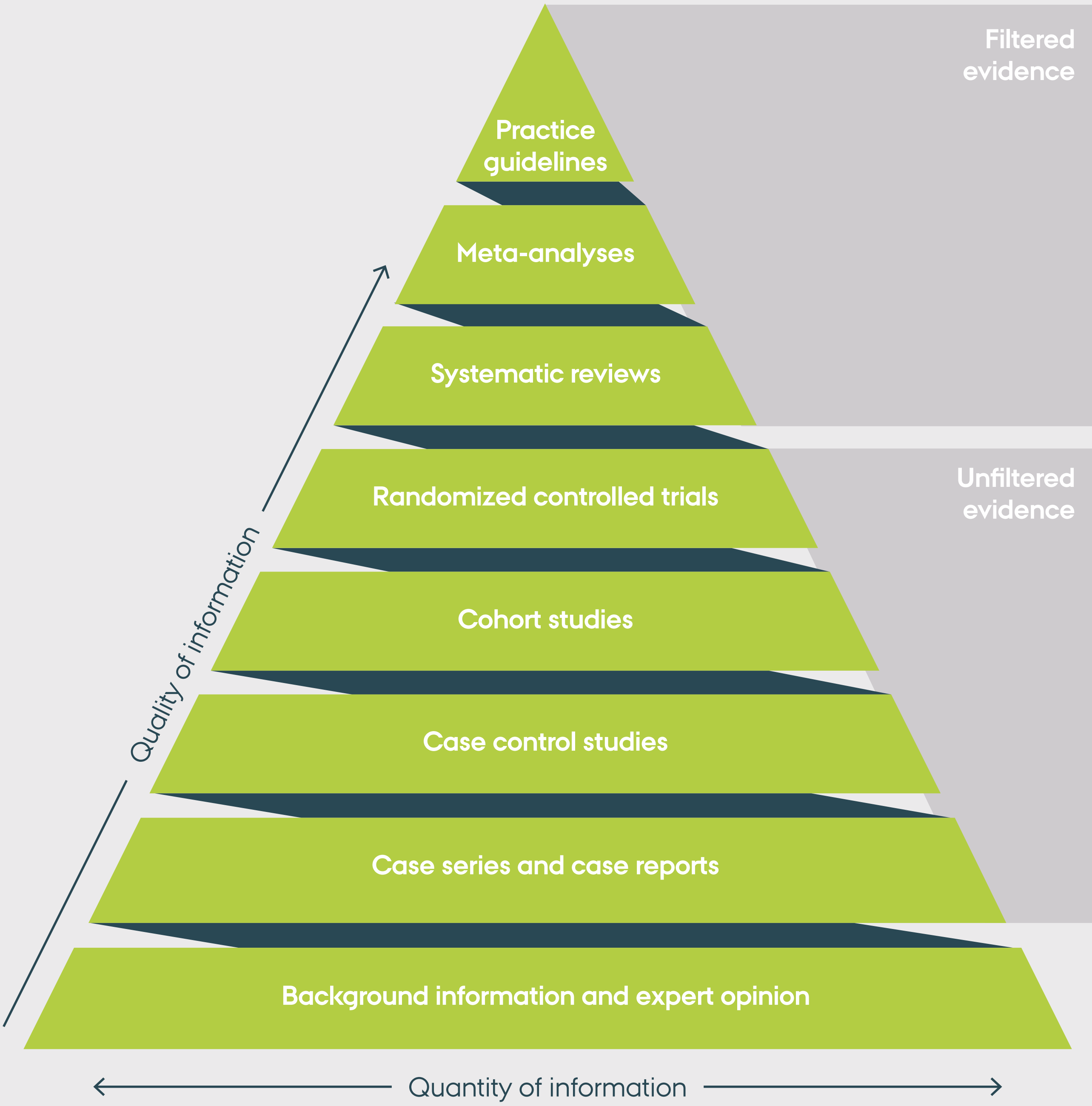
The shape of the exposure-response function provides crucial information. It can take various forms (linear, logarithmic, exponential, etc.) depending on the relationship between exposure and response. A **straight-line** (linear relationship) indicates that health risks increase at a constant rate with exposure. However, risks may be non-linear, increasing at varying rates with changes in exposure levels, such as bigger risk at higher exposures. For example, a doubling in the exposure could result in a tripling of the probability of the health outcomes. Sometimes no effect is observed until a threshold exposure level is reached, after which the risk increases.

Exposure-response functions have a wide range of **applications**. When the links between environmental exposures and health outcomes can be determined, they can help inform policy, standards, and guidelines to protect public health. Moreover, they can be used to determine the expected health benefits of measures to reduce nitrates in drinking water, because they allow estimation of the impact of reduced exposures. Such estimations can be further translated into economic benefits and applied in socio-economic analysis.

In order to identify exposure-response functions for environmental pollution, scientists often have to rely mainly on **epidemiological studies** (e.g., cohort and case-control studies). Epidemiological studies are observational and may be subject to residual confounding - when the outcome is explained by unknown or unobserved confounding factors. To overcome this limitation, scientists rely on systematic reviews that consider all the available evidence to reduce potential bias in the original studies. Systematic reviews and meta-analyses are indispensable in synthesizing and evaluating an expansive body of environmental health studies.

Box 2. Are you familiar with the pyramid of evidence?

Research studies can be classified by **the strength of their evidence and methods**. This figure visualizes this classification in the form of a pyramid. The top layer corresponds to the strongest evidence, while the bottom to the weakest. Notably, the bottom layer is where often most information is available. Sometimes, the amount of the highest quality evidence is insufficient to reach conclusive results. When that happens, we look for the next best quality evidence.



Source: UNE Library Services. https://library.une.edu/research-help/help-with/evidence-based-practice/the-evidence-pyramid/#:~:text=The%20levels%20of%20evidence%20can,pyramid%2C%20but%20decreases%20in%20quality

What Are Systematic Reviews and Meta-analysis?

Systematic reviews are a rigorous process of gathering and assessing all available studies related to a particular exposure-outcome pair. This process allows us to:

- **Synthesize the evidence** by comprehensively screening the literature. This reduces the risk of bias inherent in relying on individual studies and ensures a thorough examination of the existing evidence as a whole.
- **Harmonize disparate findings**. Studies often use different methods which can lead to conflicting or unclear results. Systematic reviews combine various findings to find common trends and patterns. This makes it easier to understand and interpret the overall evidence.
- **Identify research gaps** by pinpointing gaps in evidence or highlighting areas warranting further investigation, and **contributing** to the iterative process of science to guide future research efforts.

A meta-analysis is a statistical technique used to combine the results of multiple studies identified through a systematic review. Meta-analyses provide a more precise estimate of the effect size by increasing the sample size and power of the study. They combine and analyze data from multiple studies on the same topic to find overall trends and conclusions. Through statistical methods, meta-analyses provide an estimation of the overall effect size of an exposure-outcome relation, i.e, the exposure-response function. However, the results of a meta-analysis can change as they are based on the existing evidence at the time they were conducted.

Contribution of the MARCHES project

The MARCHES (Methodologies for Assessing the Real Cost to Health of Environmental Stressors) project is examining recent systematic reviews and meta-analyses on the association between **nitrate in drinking water and colorectal cancer**. These studies show mixed results, and some have faced methodological issues. For example, after they corrected errors they had made when extracting data from the original studies, the authors of one study recently reversed their results, now concluding that nitrate intake from drinking water is indeed associated with a higher risk of colorectal cancer (see *Clinical Nutrition* 41(5) p.1152, 2022). This highlights that it is crucial to carry out systematic reviews following a rigorous protocol designed to avoid making errors and introducing bias.

The MARCHES project

The Horizon Europe MARCHES project aims to advance methodological rigor and consistency in accounting for the welfare economic health costs of pollution, based on systematic reviews of health effects. It aims to calculate the impact of nitrates in drinking water and of air pollutants (which include ammonia from fertilizers) on public health and to quantify the economic benefits of reducing emissions and exposures. Establishing updated exposure-response functions is essential for accurately estimating the societal costs of pollution and highlighting the societal value of implementing mitigation measures. This will be demonstrated in case studies where MARCHES partners with public authorities in six countries (Czechia, Denmark, Estonia, Kosovo, Spain and Sweden). Learn more about the research and activities of the MARCHES project here: https://projects.au.dk/MARCHES

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