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# Bayesian Networks As a Tool for Predicting and Communicating Environmental Risks of Pharmaceuticals

- **Existing pharmaceutical risk assessment averages across an entire nation's use of a given substance**
- **However, nations may have stark geographical gradients in factors such as wastewater treatment infrastructure**
- **Bayesian networks present advantages in the probabilistic risk assessment and communication of these risks**
- **We present an example, using a Bayesian network to characterise the mixture and joint risk of two common beta blockers, metoprolol and propranolol**

## 1. Introduction

- Environmental risk of individual pharmaceuticals is traditionally characterised by a single-value risk quotient (RQ)
- Wastewater can contain a mixture of pharmaceuticals, which requires assessment of combined risk. Different models have been proposed to account for similar vs. different of action - concentration addition or response addition - but all are associated with methodological challenges
- Here we propose a simpler approach based on Bayesian network (BN) methodology: calculating the joint probability that any of the APIs in a mixture exceeds their respective PNEC and thus causes risk (RQ > 1)
- The BN can also be used for exploring changes in risk under scenarios, in this example basic (northwest) vs. advanced (southeast) wastewater treatment (Figure 1)
- Variation in factors such as dilution rate in the environment, wastewater production, metabolism and population are ignored at this stage

## 2. Methods

**(i) Risk characterisation for single substances:**

- A BN for individual APIs (Figure 2) was constructed according to TGD and EMA guidelines for the risk assessment of two common beta-blockers, metoprolol and propranolol (Figure 1a, Table 1)
- Predicted Environmental Concentrations in surface water ($PEC_{SW}$) of the two APIs were modelled as log-normal distributions for based on Norwegian sales data compiled for 2016-19 (Welch et al., 2022)
- Predicted No-Effect Concentrations (PNEC) (AstraZeneca 2017a, b) were used as safe threshold values
- A probabilistic RQ was calculated as the ratio of the PEC distribution to the PNEC distribution

**(ii) Risk characterisation for mixtures:**

- The combined risk of two APIs was calculated as the joint probability of RQ > 1 for either API:

$$\boldsymbol{P(RQ > 1) = 1 - (1 - P(RQ_1 > 1)) \times (1 - P(RQ_{2\ >}\ 1))}$$

- For comparison with more traditional approaches, the BN also included the node Sum of RQs which is applied under assumptions of similar mode of action (Concentration Addition) (Backhaus & Karlson, 2014)

**(iii) Risk characterisation under treatment scenarios:**

- WWTP removal was added as a scenario node to the BN to explore the differential effects of the two treatment regimens on risk of both individual substances and their mixture
- Two scenarios of wastewater treatment were applied:
  - "Basic": mechanical treatment; used across the west coast; removes 25-50% of metoprolol and 0-25% of propranolol
  - "Advanced": mechanical + chemical + biological treatment; employed largely in the south; removes 75-100% of both metoprolol and propranolol
- Mean removal rates for metoprolol and propranolol were not available for Norway, and therefore based on data from German WWTPs (Maurer et al. 2007)

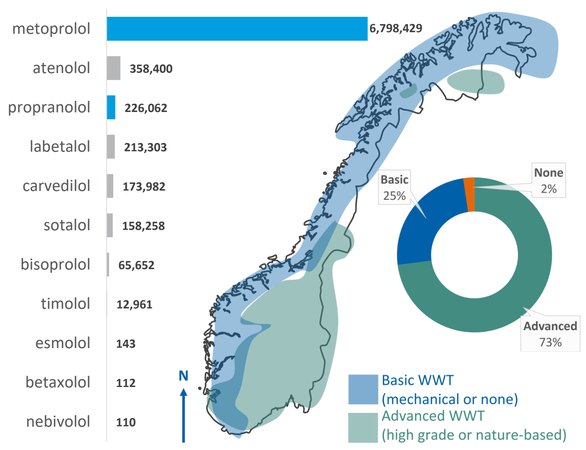
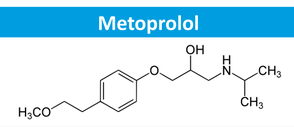
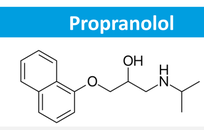



**Figure 1:**
**(a)** Consumption of beta blockers in Norway, 2019 **(g)**;

**(b)** approximate map of Norway, with areas of WWTP type coloured, Based on Berge & S. Sæther (2020);

**(c)** Wastewater treatment plant access in Norway

**Table 1:** Molecular structure, description, application, Predicted No Effect Concentrations and occurrence in Europe of metoprolol & propranolol

| API | Metoprolol | Propranolol |
|---|---|---|
| **Structure** |  |  |
| **Type** | selective β1 receptor blocker | non-selective β1 receptor blocker |
| **Indications** | high blood pressure, arrythmia, angina, heart failure, post-heart attack treatment | high blood pressure, arrythmia, angina, heart failure, post-heart attack treatment |
| **PNEC** | **7.3 µg/L** (AstraZeneca, 2017) Acute toxicity to green algae, AF = 1000 | **0.23 µg/L** (AstraZeneca, 2017) Chronic toxicity to sea urchin, AF = 10 |
| **Surface Water Occurrence (µg/L )** | **0.0003 – 9.5** (Yi et al., 2020) | **0.0001 – 0.59** (Yi et al., 2020) |

## Basic Treatment

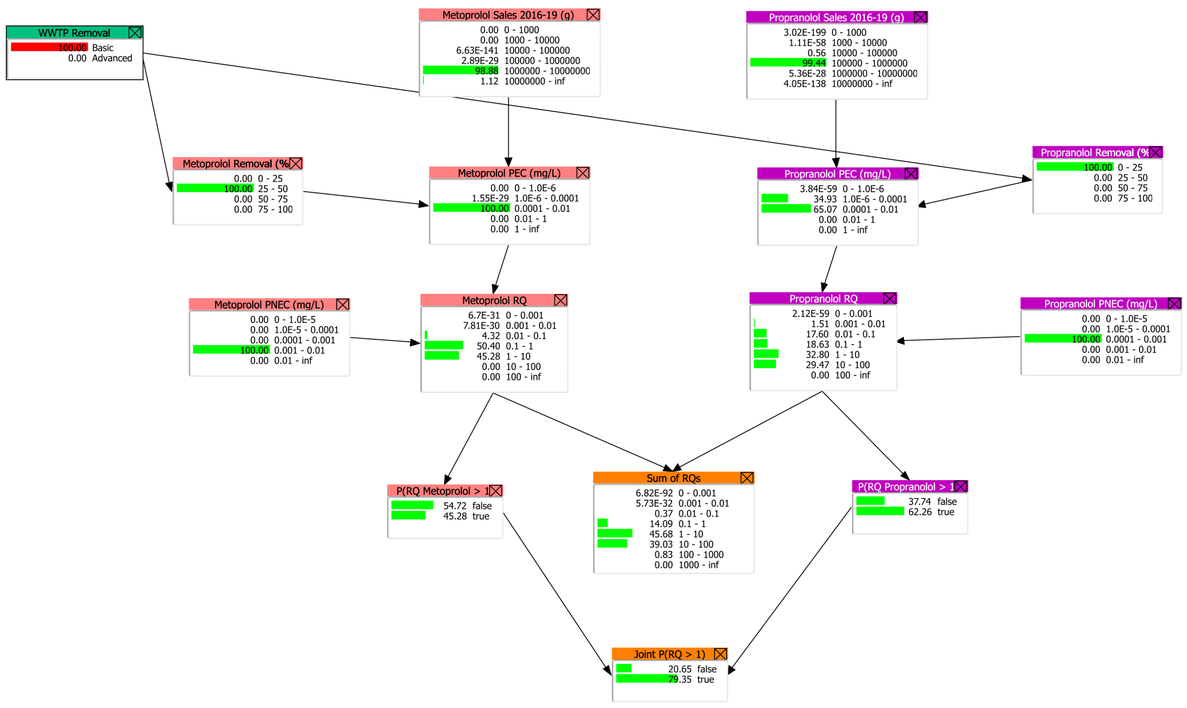



**Figure 2a:** Predicted mixture and individual environmental risk of propranolol and metoprolol in Norway, under basic WWTP conditions

## Advanced Treatment

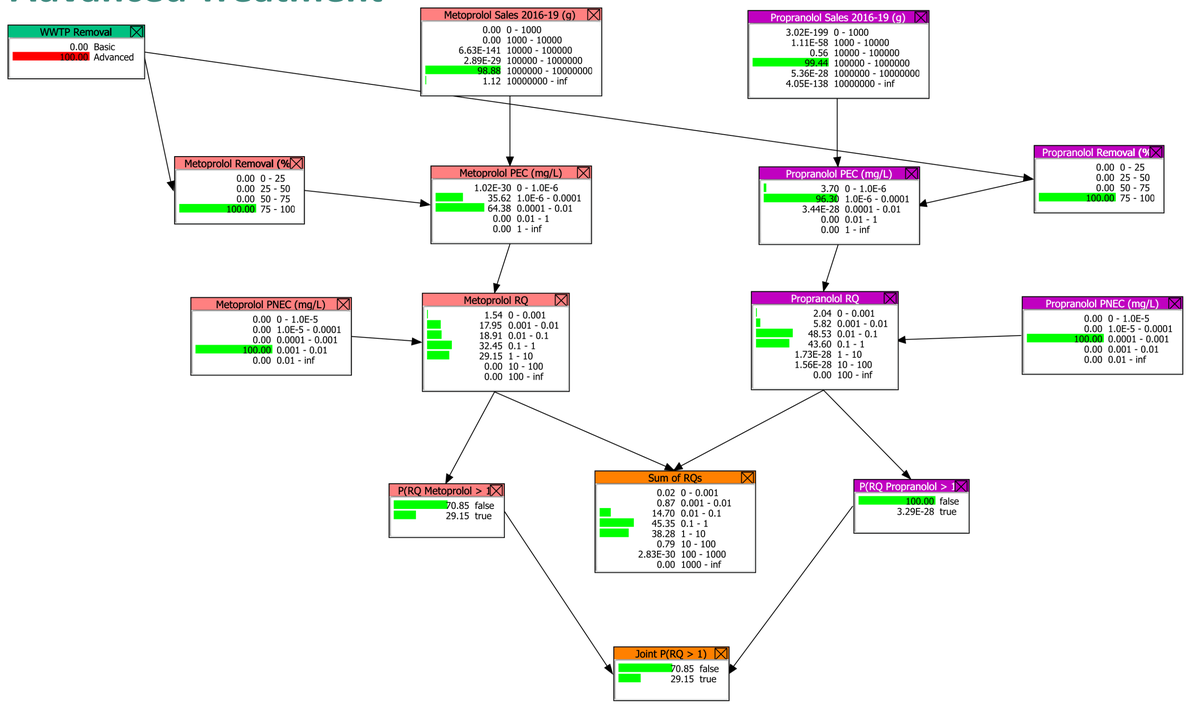



**Figure 2b:** Predicted mixture and environmental risk of propranolol and metoprolol in Norway, under WWTP conditions

## 3. Results

- Under basic wastewater treatment (Figure 2a), there is a moderate probability (45% and 62% respectively) that concentrations of metoprolol or propanol individually will exceed the safe threshold
- However, there is a high joint probability (80%) that either or both APIs exceed this threshold
- Advanced wastewater treatment (Figure 2b) reduces component probability of exceeding PEC to 29% and 0% respectively, giving a joint probability of 29% of exceedance
- The cumulative risk and the effect of treatments are also reflected in the node "Sum of RQs". However, the Sum of RQs is may be difficult to interpret, as it results from addition of fractions with different denominators, and the PNECs for metoprolol and propranolol are based on different species

## 4. Discussion & Conclusion

- Assuming no net metabolism of propranolol and metoprolol, use of advanced WWT approaches reduces joint probability of exceedance from 79% to 29%
- The assumed 10-fold dilution for Norwegian fjords is lower than reported from modelled New Zealand fjords (Plew et al, 2018), and may somewhat overestimate the PEC and therefore risk
- WWTP upgrades are then an important mitigation tool for reducing API, although even under advanced conditions overall risk to the environment will remain cause for concern, especially when more complex mixtures, rising consumption and other stressors are considered
- Our study demonstrates that Bayesian networks can provide a simple, transparent and intuitive method for calculating the both joint risk threshold probabilities and probabilistic combinations of risk for multiple substances, without the need to define the mode of action or dose-response curves.
- This BN structure can be extended to include more APIs and different scenarios, for example climate or demographic scenarios.

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**NIVA Ecotoxicology**

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