Summary

We propose a process-based approach to understand effects of mixtures that is based on the Dynamic Energy Budget Theory. We show that this approach to assess effects of mixtures is not only feasible but also has major advantages over the approaches that were commonly used thus far. The DEB based approach considers toxic effects as processes in time, and by following the time course of toxic effects valuable information can be obtained about the underlying toxic mode of action. In this thesis the emphasis was on effects on survival, but we have also shown that it is possible to predict sub lethal effects of mixtures on growth, reproduction and survival within the same consistent theoretical framework.

Mixtures are important because in real life ‘there is no such thing as single chemical exposure’. Over the last years there is a growing interest in effects of mixtures and a lot of experimental effort is put in assessing effects of mixtures. The emphasis in experimental effort thus far was in finding statistically significant synergistic interactions in mostly binary mixtures. With a synergistic interaction the effect of one compound in a mixture is enhanced by the other compound(s) in the mixture, relative to some standard model. Synergistic interactions can be important, but strong synergistic interactions are scarce. The very important question why these interactions occur is not answered by a statistical approach, in addition we have shown that statistical interactions may vary greatly at different points in time, which can not be understood by the current approaches. Even worse, small random errors can greatly influence the outcome of a test. But even more importantly the standard approaches do not allow extrapolations, which is much needed in assessing effects of mixtures as it is impossible to experimentally assess effects of even a tiny fraction of all possible mixtures. Our approach allows extrapolation to compounds where experimental data are scarce or missing, to other points in time (from acute to chronic effects and vice versa) or even potentially to other organisms.

We have shown that our approach has strong predictive power and uses very few parameters. This predictive power was not only shown under laboratory conditions but was also shown in the assessment of effects of actually measured complex mixtures in Dutch surface waters, containing over 80 different components. It was possible to predict whether or not in situ exposed waterfleas Daphnia magna could survive or would die given the actually measured mixture. In case of mortality it was possible to make a direct link to the compound or group of compounds responsible for the effect. Such knowledge is of great importance in water management, and it shows that relatively few compounds are the major cause of effects on the survival of the daphnids. Predictions of this kind are impossible to make with the AC/IA approaches because of the impossibility to extrapolate these methods to different exposure times.

An important assumption in our approach is the existence of a No Effect Concentration (NEC) and this NEC can be shared by the different constituents making up the mixture, which was experimentally verified. This is an important finding as it explains why mixtures can show effects in concentration ranges where the individual compounds making up the mixture do not show effects. We have shown that in mixtures as occurring in Dutch surface waters effects on survival of Daphnia magna can be expected at the level of the maximum permissible concentration, thus showing that current legislation has major shortcomings.