

RAXXIN - A NEW GENERATION OF ANTICOAGULANT RODENTICIDES

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Rats - A worldwide threat:

Rats live in highly socialised packs of up to hundreds of animals which care for and assist each other. Rats are highly fertile and have a life span of up to two years. The offspring of one single female rat counts up to > 1000 siblings per year. In consequence: the global human to rat ratio is estimated 1:3 to 1:4. This ratio is constantly increasing.

Rats can adapt to almost any environment. When endangered e.g. from shortness of food, they migrate even over long distances. Having found better conditions they settle and rapidly grow up to form new tribes of up to several hundreds of animals. Lately, rat plagues have been reported from the countryside as well as big cities and world capitals like Berlin, London, New York etc.

Rats are responsible for huge agricultural damage either by consumption of food or by contaminating food stocks with their excrements. This accounts for damage of an estimated 10% to 25% of the worldwide food and feed stock each year. They also cause billions of dollars of structural damage to buildings and other infrastructure (fundaments, pipes, tubes etc.) annually. Last but not least, they are vectors to and transmit a large variety of diseases, some of which with high mortality rates predominantly in regions with poor hygienic standards

Development and effects of rodenticides

Rats have been fought without significant success with "rat poisons" like arsenic, cyanides or E 605. However, such types of direct poisons do kill single rats but are unable to effect or to control the size of a whole rat population.

Rats are shy of new food sources. They prefer to sample, wait and observe whether it makes sick or causes death. In case one companion rat dies after having taken up food from a new source they identify this food source as the cause and avoid it. As a conclusion in the case one companion rat succumbs after feeding from an unknown source in a temporal connection, fellow rats will refuse to take up food from this new source. This is why rat's social behaviour protects them from being poisoned. During the past 60 years, coumarin (warfarin e.g.) and indandione type rodenticides have been outstandingly successful. They prevent the synthesis of coagulation proteins (factors) by interrupting the vitamin K cycle. After ingestion of such a vitamin K antagonist rodenticide, the existing coagulation factors are depleted in a time dependent fashion and no new ones are resynthesized. As a consequence, the rats succumb from fatal spontaneous or injury related bleeds only after a long time delay. It is for this time delay that rats do not get a chance to identify the bait as the reason for their fellow's fatality.

The phenomenon of rodenticide resistance

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Unfortunately, since the introduction of vitamin K dependent rodenticides (>60 years ago) many rat tribes have become resistant against the vitamin K antagonists. This means a huge selection advantage and those resistant rats spread out more rapidly than nonresistant rats. Today in many regions of the world (the Rhein-Ruhr area or regions south of London like Sussex etc.) almost every rat is resistant against rodenticides based on 1st coumarins and such regions are constantly growing in size and numbers..

To overcome coumarin resistance, more powerful agents and indandiones (so called super warfarins) have been developed. They also act as inhibitors of the synthesis of coagulation proteins by interrupting the vitamin K cycle. The effectiveness of those 2nd generation rodenticides is also increasingly affected by the development of rodenticide resistance in rat populations. In fact, resistance today is reported from almost all 2nd generation rodenticides except two: brodifacoum and difenacoum.

Further limitations of current rodenticides

Major disadvantages limit the widespread use of the remaining effective 2nd generation rodenticides;

1. Cross-toxicity with other animal species like dogs or birds: cross toxicity means that the poison is not specific for the targeted animal only but may be lethal for other species as well. It does not only extend to other animals that accidentally take up the rodenticide bait but also to animals that hunt or scavenge the dead corpses of poisoned or dead rats.
2. Extremely long half-life time of such rodenticides: Vitamin K substitution may serve as a rescue method by antagonizing the effect of coumarin and indandione type rodenticides. However, for 2nd generation rodenticides the outstandingly long half-life of up to one year prevents that such animals accidentally poisoned can be saved by vitamin K substitution.
3. Environmental persistence: Such rodenticides when brought out into the environment, cannot be degraded by nature resulting in environmental persistence and enhancement of such agents in e.g. soil for many years, The poisoning of the water and accumulation of the poisons in fish bringing those 2nd generation rodenticides back into the food chain.

It is for these unfavorable properties, that the approval of 2nd generation rodenticides is largely restricted to bait boxes and inhouse use only. In addition, they are strictly limited to the use by expert people. Such 2nd generation rodenticides may not be brought out into the environment. Also, 2nd generation rodenticides have been approved in Germany and the EU only for limited time frames. These approvals will be suspended, once better agents with more favorable properties, e.g. environmentally friendly rodenticides, become available

BIORoxx's mission: A new generation of compound anticoagulant rodenticides (RAXXIN)

This new class of rodenticides is composed from different small molecules which act synergistically but by themselves are nonlethal, even in very high doses. Rat toxicity of such nontoxic components is generated only, when they are ingested by rats as a compound. The compound contains each of those agents in a dose which results in toxicity by their synergistic modes of action.

- The lethal effect of RAXXIN, like with the 1st and 2nd generation rodenticides, is spontaneous or provoked bleeding.

- Each component of the compound rodenticide RAXXIN is a small, chemically defined molecule which in adequate doses can also be used for therapeutic purposes in human medicine.
- Component of RAXXIN are anti-thrombotic agents and/or platelet inhibitors and agents increasing the synergistic effect. This is the major difference compared to the classical anticoagulant type of rodenticides which work via interruption of synthesis of coagulation factors resulting in depletion of such factors.
- The chance for development of resistance is very low if not neglectable.
- None of those molecules by themselves is able to cause animal death, except when ingested or long time in very high doses.
- The resulting mechanism of the different agents (i.e. when packed into a bait and ingested simultaneously) leading to death is lethal bleeding. Hence, rat toxicity is only generated when the different agents are acting synergistically together
- Every single component of the novel new generation rodenticides is a small molecule that can be synthesised in large quantities at reasonable costs.

The major advantages of a compound rodenticide like RAXXIN:

- Each component by itself is nontoxic even in high doses. By the different modes of metabolism for each of the substances, the compound over time loses its toxicity. Hence, the remaining substances in the poisoned respectively killed rats is no longer toxic to predators and scavengers. In consequence cross toxicity to predators and scavengers is minimized or even neglectable.
- By their differential modes of metabolism, the compound loses its toxicity when excreted in feces and urine. In consequence: as the substances are metabolized by the target animal to nontoxic molecules. This minimizes also environmental toxicity.
- Each of the agents when exposed to the environment will rot and degrade and hence vanish rapidly. In consequence, such new generation rodenticides are environmentally non persistent and by that very environmentally friendly.
- With the composition concept of such 3rd generation rodenticide baits, most if not all of the objections from the regulatory authorities towards the existing rodenticides are positively addressed.
- Further developmental potential is recognized by using modern technologies to modify the molecule in a way that it better fits to other rodents. such as mice, beaver and rabbits, the later - without natural enemies - have become a rapidly growing plague in Australia.

Market situation

In 2013, global rodenticide sales were at 750 million USD, in 2020 1,3 billion USD. In the different regions of the world they are expected to grow by 10 – 25%/year. Hence the market forecast exceeds 2 billion USD in 2025

2nd generation rodenticides (e.g. brodifacoum or difenacoum) for their severe limitations have received only limited approval, limited both in time (max. 5 years) and fields of application. According to the German Federal Environmental Agency (UBA), approval will be suspended (at least in the EU), once better rodenticides with more favorable properties become available.

Worldwide patents have been filed and will provide market protection until at least 2034. Extension of patent protection can be reached from SPC's and further new patent applications.

Further beneficial facts

Since the 3rd generation rodenticides meet an urgent unmet need, there is an option to get support by the German “Umweltbundesamt (UBA)” (German Federal Environmental Agency) for the development and testing of the compound rodenticide. Also with successful development fast track approval of the 3rd generation rodenticides may be expected.

NRW Founders Grant: The CEO of BIORoxx GmbH, Astrid Gulba, has been awarded a founders grant from the federal state NRW.

INVEST – Grants for investors: The Bundesamt für Wirtschaft und Ausfuhrkontrolle (BAFA) has granted BIORoxx GmbH eligibility for the INVEST funding program which gives investors based in the EU an immediate 20% tax-free investment return of their investment. Additionally eligible investors also benefit from the flat-rate taxation of capital gains earned with an exit of such an investment at the time of exit (Deadline for applications for participation of investors in the INVEST program is 2nd December 2020).

(https://www.bafa.de/DE/Wirtschafts_Mittelstandsfoerderung/Beratung_Finanzierung/Invest/invest_node.html)

Patent situation:

Patent granted:	Australien, Canada, Israel, Korea
Patent pending:	Brasilien, China, Eurasien, Europa, Japan, Mexico, USA

