Mini Review

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Adverse effects, studied on ants, of six products largely used by humans; a mini review

Abstract

Working on ants as models, we examined the side effects of six largely used products, separately published our findings, and here summarize them for the readers' convenience. The herbicides, the active substance of which is pelargonic acid, must be used only for not cultivated area since they impact the live of the soil fauna. Imodium, the active substance of which is Loperamide, used to stop diarrhea, should be used during short time periods, monitoring the patients as for their food consumption, locomotion, social relationships, cognition and dependence on the drug use. Only small amount of the myorelaxant Epsipram, the active substance of which is Tetrazepam, should be used, monitoring the patients as for their activity, locomotion, social relationships, stress, cognition, memory and dependence on the drug consumption. The antiemetic Motilium, the active substance of which is Domperidone, should be used after having made an adequate clinical examination of the patients, take then care of them monitoring them as for their health since side effects may occur. The dietary supplement Cognizing, the active substance of which is citicoline, should not be used, being inefficient and causing stress, agitation, nervousness and strong dependence on its consumption. The dietary supplement PQQ is efficient and has no adverse effect; it could be used, but at low doses, since, being novel, some not yet observed side effects may occur.

Keywords: cognizing, domperidone, herbicide, imodium, loperamide, motilium, PQQ, tetrazepam

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Abbreviations: ang deg, angular degrees; ang deg/cm, angular degrees per centimeter; mm/s, millimeter per second; n°, number; n^{os}, numbers

Introduction

Working on ants as models, we have until now studied the effects of 56 products or situations used by humans. Though having duly separately published our successive works, we moreover published up to now seven summaries of these studies for the readers' convenience.[1–7] The last six products we examined are not included in these summaries. This is why we here briefly report our findings on these six last studied products not yet related in a summary. These six products are, in the order of their studies and of their present brief report, an herbicide still authorized, easily available and largely used; three drugs largely consumed by humans their use being still debated; two dietary supplements rather new and more and more consumed by humans. Before relating our results, we here below give available information on each of these six products, in the order we studied them and briefly here report our findings.

Pollution due to herbicides is far less examined than that resulting from the humans' use of pesticides, insecticides and drugs. However, since they prevent plants living, herbicides are likely to affect the health of contaminated animals. There exist many kinds of herbicides, with different chemical structures, affecting different biological functions of the plants, differently acting. Their use leads to a decreased of weeds, and of birds.[8,9] They pollute natural water,[10,11] and cause illness in humans.[12–17] The most dangerous ones are no longer authorized in several countries. Those, the active substance of which is pelargonic acid, are still authorized. However, even if pelargonic acid is a natural substance present in nature, it may also have several adverse not yet known effects. We thus aimed, to study on ants as models, the effects of a largely used and easily available herbicide of this kind, Herbatak. Pelargonic acid attacks the cellulose wall of the plants which finally died. It affects humans' skin and eyes. Noting else is known as for its potential physiological and ethological adverse effects, and we thus intended to at least partly fill this gap.

Imodium is an easily available drug allowing efficiently treating diarrhea, acting on the nervous system innerving the colon.[18–20] Its active substance is Loperamide which has a chemical structure similar to that of opiate receptors antagonists. It does not cross the blood-brain barrier, has no analgesic effect,[21] and according to some authors has no significant adverse effect.[22] However, side unwanted effects are reported by other researchers,[23–26] as well as in the notice for use joined to the Imodium packages (e.g., headache, dizziness, drowsiness). Estimating that not enough information can easily be found by practitioners and patients about such a largely used and easily available drug, we decided to study, on ants as models, the potential ethological and physiological adverse effects of Imodium.

The benzodiazepine Tetrazepam is the active substance of drugs (e.g., Epsipam) allowing decreasing painful muscular contractions.[27] It is efficient, has only few adverse effects,[28–30] but more trials should be conducted for having an obvious idea about its safety.[31,32] A bibliographical study also concludes that more clinical trials are required. [33] In the notice for use joined to Epsipam packages, several adverse effects are reported, such as memory and behavioral impairments, aggressiveness, skin allergy, dependence. Consequently, to get the bottom of it, we aimed to examine, on ants as models, the potential impact of Epsipam consumption on several biological traits.

Domperidone is the active substance of the antiemetic drug Motilium. It is very efficient in numerous cases of health problems, among others, for children, adults, patients under chemotherapy or pulmonology treatment, women in menopause, all this with few adverse effects.[34–42] However, Motilium induces some side effects such as headache, anaphylactic shock, anxiousness, dizziness, drowsiness, asthenia, akathisia. In some European lands, it is no longer authorized

for children. To have an opinion about this decision, and because nothing is reported as for the impact of Motilium on several important ethological and physiological traits, we intended to examine on ants as models such potential impacts of this drug.

Several dietary supplements contain essentially citicoline (cytidine-diphosphate-choline) and for instance a small amount of PQQ (e.g., Cognizing). Citicoline could ameliorate the brain functioning,[43] and help patients recovering after having had an ischemic stroke or other neurological disorders,[44–47] but these properties are not unanimously affirmed. Nevertheless, citicoline has a neuroprotective effect,[48] and ameliorates the memory in case of deficiencies,[49] thanks to its increase of choline in the cell membrane.[50–55] It is also beneficial to persons suffering from glaucoma,[56] and is very useful for caring of elderly persons.[57] All this is again related in three reviews.[58–60] Due to such very probable beneficial effects of citicoline, dietary supplements containing essentially this substance were created and sold to humans for improving their brain functioning. Because the wanted effect of such dietary supplements might not occur, and because only very few side effects due to their consumption are reported, we decided to study on ants as models the impact of Cognizing on several physiological and ethological traits, including memory, sensory perception, social relationships.

PQQ (pyrroloquinoline-quinone) is a co-enzyme present, among others, in the inner membrane of the mitochondria, and it valuably improves the functioning of this cellular element. Drugs and dietary supplement having PQQ as active component have been created and their beneficial impact on, among others, the mitochondria have been many times proved, e.g.[61–64] PQQ was also found to be beneficial to rats having had a cerebral artery occlusion.[67] It also helps caring of persons suffering from diabetes.[65] However, even if its mode of action becomes more and more elucidated over time, not all its beneficial effects are until now known, and nothing is not yet known about its potential side unwanted effects. We thus opted to study on ants as models the potential physiological and ethological wanted and unwanted effects this dietary supplement may present.

Why using ants, which species we used, what we know on it, and which traits, potentially affected by the examined products, we considered is explained in each of our works. We here only briefly recall the answers to these questions. The basic biological processes are similar in all animal species (genetics, nervous influx, muscles contraction, sensory perception, conditioning acquisition). They are thus, at least in a first time, studied on vertebrates and invertebrates, the latter being often preferred for their small size, easy maintenance in a laboratory, and short reproductive cycle. Hymenoptera (e.g., bees) are largely used, and ants can thus be used. They can be the more so because their maintenance is very easy, cheap, even if several colonies containing hundreds of individuals are required. We work on the species *Myrmica sabuleti* Meirnert, 1861, the biology of which we know rather well, having investigated, among others, on their visual perception, navigation, recruitment,[66] ontogenesis of some of their skills, self-recognition in a mirror, distance and size effects,[69] Weber's law,[68] numerosity abilities and related topics (e.g., [69–71]). This ant species represents thus, at last for our research, a comfortable biological model.

Material and methods

There are explained in each of our works, those relative to the six here briefly reported ones,[72–77] as well as in all the previous 56 ones. We thus here only cite these methods and very briefly explain them.

Collection and maintenance of ants

The ants were collected in autumn and spring 2021 and 2022, in Belgium, in Ardenne and in Condroz, from abandoned quarries, under stones and in grass. The ant colonies contained about 500 to 1,000 workers, 1 to 3 queens and brood. In the laboratory, they were kept in 1 to 3 glass tubes half filled with water, a cotton plug separating the water from the place devoted to the ants' nesting. The nest tubes of each colony were set in a tray the borders of which having been covered with talc. These trays served as foraging areas: food was there delivered (larvae of *Tenebrio molitor* three times per week; sugar water delivered in small plugged tubes), and experiments were performed in these trays. The lighting varied between 330 and 110 lux, the humidity always equaled 80%, the temperature constantly equaled 20°.

Products provided to the ants

The herbicide, at the concentration advised for humans' use, was spilled on the bottom of the trays around the food and the nest entrance. The other products were provided to the ants at the adequate concentration (10 times more than that advised for humans) in their usual sugar water given in their usual sugar water tubes. The cotton plugs of these tubes were refreshed, and their entire contents were renewed as necessary. Control experiments were firstly conducted on ants normally maintained. Then, the product, the effects of which must be studied, was provided to the ants, and the test experiments started 12 to 24 later.

Assessment of ants' traits potentially affected by the delivered products the effects of which must be examined

The ants' food consumption and activity were assessed by separately counting several times per day, during six days, the ants being on their meat, at their sugar water tube entrance, and active at any part of their territory, by establishing the daily means of these counting, and finally the mean of these six daily means. The ants' linear speed, angular speed, and orientation were assessed by recording ants' trajectories and analyzing them thanks to adequate software, then establishing the median and the quartiles of the recorded values. The ants' audacity was evaluated by counting those coming onto an unknown apparatus, and establishing the mean and extremes of the recorded numbers. The ants' tactile perception was quantified by assessing their linear and angular speeds while they walked on a rough substrate (if perceiving the uncomfortable character of such a substrate, the ants walk more slowly and sinuously as usual), and by establishing the median and quartiles of the obtained values. The ants' brood caring was quantified by removing larvae from the nest, then counting those among ten ones not yet re-entered over time. The ants' social relationships were quantified by counting, in the course of dyadic encountering, the number of times an ant of the pair did nothing (level 0), contact the opponent with its antennae (level 1), opened its mandibles (level 2), gripped the opponent (level 3), tried to sting or stung the opponent (level 4). The results of ten experiments were correspondingly added, and a variable 'numbers of levels 2 + 3 + 4 / levels 0 + 1' was each time calculated. The ants' state of stress and cognition was evaluated by counting those escaped over time from an enclosure, and correspondingly adding the results of several experiments. The ants' cognition was evaluated by counting those having and having not be able to cross a twists and turns path over time, and correspondingly adding the numbers obtained during several experiments. The ants' learning and memory was appreciated through their ability to acquire conditioning, then their loss of it after

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the cue removal, and by adding the results of two such experiments. The cue was a blue or green or yellow hollow cube set near the food. The ants' adaptation as well as habituation to the side as well as the wanted effects of a product were assessed by quantifying, several days after having lived with this product, one or a few traits affected by the product, and comparing the results with those obtained soon after the ants lived with the product. The decrease of the effect of a product was studied by replacing at a given time the product solution by the ants' usual sugar water, and quantifying over time one or two traits affected by the product until the obtained values equaled those corresponding to ants normally maintained. The mathematical function of such a decrease was tried to be defined.

Remark

The here given table is new. The photos are never published ones: taking several photos of each experiment, we could select not yet published ones.

Table 1 One of the side effects of six products largely used by humans. Of course, each product except PQQ, have several other side effects given in the text together with their wanted effect. Each product has been separately studied and the obtained results separately published. Each reported effect has been statistically checked as for their significance. n°: number

Product and examined trait	Ants normally maintained	Ants in presence of the product
Herbatak: learning.	85%	45%
conditioning score		
Imodium: meat intake	1.02	0.27
mean n° of ants on the meat food		
Epsipam: audacity	2.3	0.98
mean n° of ants on an unknown apparatus		
Motilium: activity	14.98	6.21
mean number of active ants		
Cognizing: sinuosity of movement	109 (100-123)	132 (113-156)
angular degrees /cm, median (quartiles)		
PQQ: sugar water consumption	0.5	0.69
mean n° of ants on the sugar water		

Results

The herbicide Herbatak

The herbicides are a kind of products, used by humans, which pollute the environment and are not studied to a large expend as are insecticides and drugs. The most toxic ones are no longer authorized. Those the active substance of which is pelargonic acid can still be used. We studied the side effects of one of them, largely used and easily available: herbatak®. On ants, this product decreased the food consumption, orientation, audacity, tactile perception, social relationships (Figure 1), cognition, learning (Table 1) and memory. No adaptation occurred to these side effects. The effect of Herbatak® vanished in 24 hours after its used was stopped. On the basis of these results, it can be deduced that the fauna of the areas treated with such kind of herbicides is impacted, and has its health even its life imperiled. In other words, though duly weeded, such treated areas have their fauna affected and may even be deprived of their fauna which is essential for efficiently cultivating. We thus advise to use herbicides the active substance of which is pelargonic acid only for not cultivated areas e.g., (sidewalks, driveways, parking lots) and never for areas on which plants are cultivated (e.g., gardens, areas with cultivated fruits and vegetables). We also advise to do so avoiding polluting the environment and the natural water, as well as taking care of the users' health (e.g., their eyes and skin).

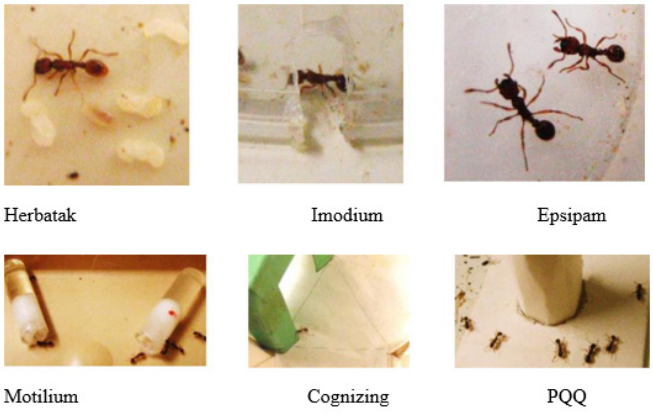

Figure 1 For each product, a photo of one of their side effects, except for PQQ, the photo being that of a wanted effect. Of course, each product had many other not illustrated effects reported in the text. Herbatak: decreased the ants' brood caring; Imodium: decreased the ants' ability to escape from an enclosure, so their cognition; Epsipam: induced some aggressiveness towards congeners, impacting thus the social relationships; Motilium: leaded to dependence on its consumption (the tube with a red dot contained the drug); Cognizing: did not affect the ants' conditioning acquisition; the ant duly responded to the learned green cube; PGG: increased the number of ants coming onto an unknown apparatus, and thus their activity and audacity.

Imodium

Imodium is an easily available drug which allows efficiently treating diarrhea. Its active substance is loperamide, an opiate derivative. Few adverse effects of it are commonly reported, but not easily available bibliography informs that it has some important side effects and can lead to abuse. We thus examined on ants as models the potential side effects of Imodium, and found that this drug affected the food consumption (Table 1), locomotion, audacity, social relationships, cognition (Figure 1), learning and memory. No adaptation occurred to these side effects, and strong dependence developed. The effect of Imodium vanished in about 13 hours after weaning. On the basis of its efficiency and of the adverse effects we found, we advise to treat patients suffering from diarrhea thanks to Imodium, but to do so during the shortest possible time period and to monitor them as for their food intake, locomotion, social relationships, cognitive abilities and dependence of this drug consumption. Concerning the last advice, it must be noted that Loperamide consumption is increasing in the United States since high dose of this substance can lead to euphoric effects.[78] Consumers should thus be monitored as for their health and their potential increase of Loperamide consumption.

Tetrazepam (Epsipam)

The myorelaxant drugs, the active substance of which is Tetrazepam (e.g., Epsipam), are no longer authorized in some European lands, but are still largely used in other countries. In order to have a personal opinion about these two different directives, we studied on ants as models, the ethological and physiological potential side effects of Epsipam. Effectively, this drug impacted the ants' food consumption, activity, orientation, audacity (Table 1), sensory perception, social relationships (Figure 1), state of stress, cognition, learning and memory. Adaptation to such side effects occurred, and ants developed dependence on Epsipam consumption. On the basis of these results, we concluded that the European withdrawing is valid. However, drugs containing Tetrazepam are more efficient than the other kinds of myorelaxants. Therefore, we propose to treat patients

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with such efficient drugs, but using the smallest possible dose during the shortest possible time period, and to monitor the patients as for the occurrence of the side effects we revealed in ants, e.g., impairments of activity, locomotion, social relationships, stress, cognitive abilities, memory and dependence on the drug consumption.

The antiemetic Motilium

Motilium, the active substance of which is domperidone, is an efficient largely used antiemetic drug, which is nowadays no longer authorized in France. Several of its side effects are divulgated, but nothing is mentioned about important potential physiological and ethological impacts. We thus studied such impacts on ants as models, and found that Motilium affected these insects' food consumption, activity (Table 1), locomotion, orientation, audacity, sensory perception, social relationships, state of stress, cognition, learning and memory. No adaptation to these side effects occurred, and ants developed dependence on Motilium consumption (Figure 1), the effect of which vanished in about 12 hours after weaning. Clinicals analysis now exist to predict if patients will strongly suffer from side effects of Motilium.[42] Since this drug is really very efficient, we propose to still use it, but after having made the required medical exam, then, to treat the patients with the smallest possible dose and during the shortest possible time period, and to simultaneously monitor them as for the occurrence of the here reported side effects, such as a decrease of activity, some locomotor function disfunctioning, social relationships impairments, increase of stress, dependence on the drug consumption.

Cognizing

Cognizing is a dietary supplement, the active substance of which is citicoline, a drug allowing caring of persons suffering from cerebral disorders. It is thus used for potentially improving the brain functioning of human adults. Dietary supplements are not always effectively efficient, are often expensive, and may present some side effects. We thus studied on ants as models the potential wanted and side effects of Cognizing. We discovered that this dietary supplement caused stress, agitation, and nervousness, and consequently impacted the ants' food intake, locomotion (Table 1), orientation, audacity, and social relationships. It did not affect the ants' sensory perception, cognitive abilities, and memory (Figure 1). It may slightly improve the ants' memory. No adaptation to the side effects occurred, as well as no habituation to the wanted effect occurred. The ants developed a strong dependence on Cognizing consumption, and the effect of this dietary supplement rapidly vanished after weaning in a total of only 11 hours. To conclude, Cognizing is not well appropriated for rapidly improving the brain functioning; it only slightly ameliorates the memorization. Also, it presents several side effects, essentially stress, nervousness, and a strong dependence on its consumption. We do not recommend it. Many expensive dietary supplements are inadequately efficient and cause several adverse effects. Humans should pay attention while using them, and stop to use them if health problems occur. On the other hand, citicoline is an efficient drug allowing patients recovering after having had or while having some cerebral damage.

PQQ

PQQ is a recently used drug as well as a dietary supplement in order to improve humans' brain functioning and activity. Its wanted effects are rather well known, but its potential adverse ones are not yet so. This is why we studied such potential ethological and physiological side effects of PQQ using ants as biological models. It is the first time, all along our study of until now 56 products used by humans, that we found so few slight adverse effects and obvious beneficial ones. Indeed, PQQ favorably affected the ants' activity, audacity (Figure 1), cognitive abilities, learning and memory. It did not impact or very slightly affected all the other examined biological traits. In fact, PQQ increased the ants' sugar water consumption (Table 1) and sinuosity of movement. In addition, the ants did not develop dependence on this dietary supplement consumption, the effect of which regularly, linearly decreased after weaning, and vanished in a total of 33 hours. PQQ is thus not only a drug which could help caring of patients (e.g., suffering from cerebral artery occlusion or Alzheimer's disease, requiring neuroprotectant or improvement of their mitochondria functioning), but is also a promising dietary supplement allowing improving humans' (in good health) activity and brain functioning. However, all the effects of PQQ are not yet well known. Therefore, as also reported in the notice for use joined to the product package, we recommend to consume it with moderation ant to pay attention to any health problems occurrence.

Discussion

For each examined product, the results of the different conducted experiments were in agreement with each other, and were also in agreement with the observations made by practitioners, pharmacists, and other researchers. In addition, each time, we could precise previously made observations (e.g., on the decrease of the effect of the product after its consumption was stopped), and add novel or not divulgated ones (e.g., impact on food intake, social relationships, stress, cognitive abilities). For each examined product, we could finally define how using it safely, at low cost. All these novel information should be known by practitioners, pharmacists and patients. As many times previously observed (e.g.[79]), a dependence on a product developed when the effect of the product rapidly decreased after weaning. In general, for each of the six here studied products, as well as for the previously studied ones and for any other similar products, attention should be paid concerning its use, efficiency and safety, because, even if meticulous, honest and statistically significant experimental researches have been made, drugs, dietary supplements (above all) and several other products are produced with the aim to earn money, and are sold under well-organized marketing. Concerning the medicinal analysis of drugs, dietary supplements, pesticides and similar products, before experimenting on humans and even mammals, studies on ants could advantageously be made. Indeed, ants appeared to be excellent biological models, capable to reveal easily, rapidly, at low cost many physiological and ethological impacts of the product, though, of course, these studies are only the first step of the entire examination of the product.

Conclusion

For each examined product, on the basis of all our observations, we could define a procedure for use we here below summarize.

I. Herbatak (pelargonic acid): use as an herbicide; only for not cultivated area, paying attention to not contaminate other areas and natural water, as well as to the users' eyes and skin.

II. Imodium (Loperamide): use to stop diarrhea; during the shortest possible time period, and paying attention to the users' food intake, locomotion, social relationships, cognitive abilities, and above all dependence on its consumption.

III. Epsipam (Tetrazepam): use as a myorelaxant; at the smallest possible dose, during the shortest possible time period, paying attention to the users' activity, locomotion social relationships, stress, cognition, memory and dependence on this drug use.

IV. Motilium (Domperidome): use as an antiemetic drug; after having made the required medicinal analysis allowing knowing the users' potential reactions to the product, then treating them

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shortly with small amount, and paying attention to their health, side effect being susceptible to occur.

V. Cognizing (citicoline): use as a dietary supplement for "improving humans' brain functioning"; poorly efficient and induces stress, agitation, nervousness, strong dependence; to be avoided, not to use.

VI. PQQ: use as a dietary supplement for improving humans' activity and brain functioning; no adverse e ffect, efficient, recommended (but expensive).

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Conflicts of interest

We affirm having not conflict of interest as for the use of any of the here examined products. We work on ants and receive not money for making our research. We maintain the ants under the best possible conditions and collect on field the smallest possible number of colonies.

References

1. Cammaerts MC. Ants as biological models for studying effects of substances used by humans. *JSM Anat Physiol.* 2016;1(1):1003.
2. Cammaerts MC. Some findings on ants as models, which should be considered for caring of humans. *MOJ Biol Med*. 2017;1(5):125–128.
3. Cammaerts MC. Ants as models for examining potential adverse effects of products used by humans. *JSM Anat Physiol.* 2018;3(1):1016.
4. Cammaerts MC. Brief report of the effects of seven human drugs studied on ants as models. *MOJ Biol Med.* 2019;4 (2):42–47.
5. Cammaerts MC. Harmful effects of human's environmental factors and drugs, and advices for a safer live; a study on ants as models**.** *The World Journal of Pharmaceutical Sciences*. 2021;9(1):34–45.
6. Cammaerts MC. Side effects of drugs studied on ant models: a mini review. *MOJ Biol Med.* 2022;7(1):1–7.
7. Cammaerts MC. Not sufficiently revealed side effects of three largely used drugs, i.e., furosemide, Apranax, Metformin, studied on ants as models. *EC Pharmacol Toxicol*. 2022;10(6):75–83.
8. Fried G, Norton LR, Reboud X. Environmental and management factors determining weed species composition and diversity in France. *Agriculture, Ecosystems & Environment.* 2008;128(2):68–76.
9. Wilson JD, Morris AJ, Arroyo BE, et al. A review of the abundance and diversity of invertebrate and plant foods of granivorous birds in northern Europe in relation to agricultural change. *Agriculture, Ecosystems & Environment.* 1999;75(2):13–30.
10. Dubois A. *Contamination des cours d'eau par les pesticides en 2011*. Commissariat Général Au Développement Durable - Chiffres et Statistiques. 2013;436:1–7.
11. Willis GH, McDowell L. Pesticides in agricultural runoff and their effects on downstream water quality. *Environm Toxicol Chem.* 1982;1(4)**:**267–279.
12. Weisskopf MG, Moisan F, Tzourio C, et al. Pesticide Exposure and Depression among Agricultural Workers in France. *Am J Epidem.* 2013;178(7):1051–1058.
13. Dreiher J, Kordysh E. Non-Hodgkin Lymphoma and Pesticide Exposure: 25 Years of Research. *Actae Haematol.* 2006;116(3):153–164.
14. Viel JF, Challier B, Pitard A, et al. Brain cancer mortality among French farmers: The vineyard pesticide hypothesis. *Arch Environm Health.* 1998;53(1):65–70.
15. Jane A, Hoppin DM, Umbach SJ, et al. Chemical Predictors of Wheeze among Farmer Pesticide Applicators in the Agricultural Health Study. *Am J Respir Critical Care Med*. 2002;165(5):683–689.
16. Ascherio A, Weisskopf Marc G, Honglei Chen, et al. Pesticide Exposure and Risk for Parkinson's disease. *Ann Neurol.* 2006;60(2):197–203.
17. Gaspari L. Prenatal environmental risk factors for genital malformations in a population of 1442 French male newborns: a nested case–control study. *Human Reprod*. 2011;26(11):3155–3162.
18. Baker DE. Loperamide: a pharmacological review. *Rev Gastroenterol Disord*. 2007;7[Suppl]3:S11–18.
19. Ooms LA, Degryse AD, Janssen PA. Mechanisms of action of loperamide. *Scand J Gastroenterol Suppl*. 1984;96:145–55.
20. Bishop-Freeman SC, Feaster MS, Beal J, et al. Loperamide-Related Deaths in North Carolina. *J Analytical Toxicology.* 2016;40(8):677–686.
21. Smith DF, Smith CC, Douglas JG, et al. Severe Salmonellosis Related to Oral Administration of Anti-Diarrheal Drugs. *Scottish Med J.* 1990;35(6):176–177.
22. Heel RC, Brogden RN, Speight TM, et al. Loperamide: a review of its pharmacological properties and therapeutic efficacy in diarrhea. *Drugs.* 1978;15(1):33–52.
23. Hanauer SB. The role of loperamide in gastrointestinal disorders. *Rev Gastroint Disorders.* 2008;8(1):15–20.
24. Palmer KR, Corbett CL, Holdsworth CD. Double-blind cross-over study comparing loperamide codeine and diphenoxylate in the treatment of chronic diarrhea. *Gastroenterology.* 1980;79(6):1272–1275.
25. Akel T, Bekheit S. Loperamide cardiotoxicity: a brief review. *Ann Nonivasive Electrocardiol.* 2017;23(2):e12505.
26. Delwaid PJ, Pennisi G. A comparative electrophysiologic study of Diazepam and Tetrazepam in patients with spasticity. *J Neuro Rehab*. 1997;11(2):91–96.
27. Kaeser HE, Gihring H, Bergmann R, et al. Testing an anti-spasticity drug (Tetrazepam) with the Pendulum test: a monocentric pilot study. *Neurorehabilitation and Neural Repair*. 1998;12(4):169–177.
28. Simiand J, Keane PE, Biziere K, et al. Comparative study in mice of Tetrazepam and other centrally active skeletal muscle relaxants. *Arch in Pharmacodyn Ther*. 1989;297:272–285.
29. Proy-Vega B, Cano-Cuenca N, Aguitte C, et al. Requiem for tetrazepam. *Rev Neurol.* 2013;57(1):1–2.
30. Proy-Vega B, Bueso JJ, Arroyo PA, et al. PS-026 Data mining: Pharmacovigilance signal of benzodiazepines and skin and subcutaneous tissue disorder. *Patient Safety and Risk Management.* 2016;23:225.
31. Schnitzer TJ, Ferraro A, Hunsche E. A comprehensible review of clinical trials on the efficacity and safety of drugs for the treatment of low back pain. *J Pain and Symptom Management*. 2004;28(1):72–95.
32. Proy-Vega B, Aguirre C, de Groot P, et al. On the clinical evidence leading to Tetrazepam withdrawal. *Exp. Opinion on Drug Safety*. 2014;13(6):705–712.
33. Reddymasu SC, Soykan I, McCallum RW. Domperidone: review of pharmacology and clinical applications in gastroenterology. *Am J Gastroenterol.* 2007;102:2036–2045.
34. Dupont C, Molkhou P, Petrovic N, et al. Treatment using motilium of gastro-esophageal reflux associated with respiratory manifestations in children. *Annales de Pédiatrie.* 1989;36(2):148–150.
35. Reyntjens AJ, Niemegeers CJ, Van Nueten JM, et al. Domperidome, a novel and safe gastrokinetis anti-nauseant for the treatment of dyspepsia and vomiting. *Arzneimittelforschung.* 1978;28(7):1194–1196.

36. Cha JJ, Kim SK, Hyun IY, et al. Antiemetic effects of Metoclopramide and Motilium suppository in patients perceiving Cisplatin based chemotherapy: a randomized crossover trial. *J Korean Cancer Association.* 1990;22(2):307–316.

37. Vadasz I. Examination of Motilium in the prevention of gastro-intestinal side-effects of different drugs in pulmonology. *Therapia Hungaric.* 1988;36(4):202–205.

38. Huber G. Treatment of gastro-intestinal complaints accompanying menopause with Motilium film-coated tablets. *TherapyHung.* 1987;35(4):227–231.

39. Brogden RN, Carmine AA, Heel RC, et al. Domperidone. A Review of its Pharmacological Activity, Pharmacokinetics and Therapeutic Efficacy in the Symptomatic Treatment of Chronic Dyspepsia and as an Antiemetic. *Drug Evaluation.* 1982;24:360–400.

40. Schey R, Saadi M, Midani D, et al. Domperidone to Treat Symptoms of Gastroparesis: Benefits and Side Effects from a Large Single-Center Cohort. *Dig Dis Sci.* 2016;6:3545–3551.

41. Parkman HP, Jacobs MR, Mishra A, et al. Domperidone Treatment for Gastroparesis: Demographic and Pharmacogenetic Characterization of Clinical Efficacy and Side-Effects. *Digestive Diseases and Sciences* 2011;56:115–124.

42. Cano Cuenca N, Del Pozo Garcia JS, Jordan J. Citicoline efficiency on cognitive function: a systematic review. *Journal of Aging research & Clinical practice.* 2015;4(4):240–246.

43. Clark WM, Williams BJ, Selzer KA, et al. A randomized efficacy trial of citicoline in patients with acute ischemic stroke. *Clinical Trial, Stroke.* 1999;30(12):2592–2597.

44. Martynov MY, Gusey EI. Current knowledge on the neuroprotective and neuroregenerative properties of citicoline in acute ischemic stroke. *J Experim Pharmacol.* 2015;7:17–28.

45. Davalos A, Alvarez-Sabin J, Castillo J, et al. Citicoline in the treatment of acute ischemic stroke: an international, randomized, multicenter, place-controlled study (ICTUS trial). *Lancet*. 2012;380(9839):349–357.

46. Pei-yu S, Xiao-cui Z, Xiao-xue Y, et al. Early application of citicoline in the treatment of acute stroke: a meta-analysis of randomized controlled trails. *J Huazhong Univ Sci Tech*. 2016;36(2):270–277.

47. Alvarez-Sabin, J, Roman GC. The role of citicoline in neuroprotection and neurorepair in ischemic stroke. *Brain Sci.* 2013;3(3):1395–1414.

48. Fioravanti M, Buckley AE. Citicoline (Cognizing) in the treatment of cognitive impairment. *Clinical Intervention in Aging.* 2006;1(3):247–251.

49. Saver JL. Citicoline: update on a promising and widely available agent for neuroprotection and neurorepair. *Reviews in Neurological Diseases.* 2008;5(4):167–177.

50. Adibhatla RM, Hatcherr JF, Dempsey RJ. Citicoline: neuroprotective mechanisms in cerebral ischemia. *J Neurochem*. 2002;80(1):12–23.

51. Lopez Coviella I, Agut J, Savci V, et al. Evidence that 5'cytidinephosphocholine can affect brain phospholipid composition by increasing choline and cytidine plasma levels. *J Neurochem.* 1995;65(2):889–894.

52. Babb SM, Wald LL, Cohen BM, et al. Chronic citicoline increases phosphodiesters in the brains of healthy older subjects: an in vivo phosphorus magnetic resonance spectroscopy study. *Psychopharmacology*. 2002;161(3):48–54.

53. Rao AM, Hatcher JF, Dempsey RJ. Does CDP-choline modulate phospholipase activities after transient forebrain ischemia? *Brain Research.* 2001;893(1–2):268–272.

54. Conant R, Schauss AG. Therapeutic applications of citicoline for stroke and cognitive dysfunction in the elderly: a review of the literature. *Altern Med Rev.* 2004;9(1):17–31.

55. Roberti G, Tanga L, Michelessi M, et al. Cytidine 5'-Diphosphocholine (citicoline) in glaucoma: rationale of its use, current evidence and future perspectives. *Int J Mol Sci*. 2015;16(12):28401–28417.

56. Putignano S, Gareri P, Castagna A, et al. Retrospective and observational study to assess the efficacy of citicoline in elderly patients suffering from stupor related to complex geriatric syndrome. *Clin interv Aging.* 2012;7:113–118.

57. Overgaard K. The effects of citicoline on acute ischemic stroke: a review. *J Stroke and Cerebrovascular Diseases.* 2014;23(7):1764–1769.

58. Secades JJ. Citicoline: pharmacological and clinical review. *Rev Neurol*. 2017;63(S03):S1–S73.

59. Jasielsi P, Piedel F, Piwek M, et al. Application of citicoline in neurological disorders: a systematic review. *Nutrients.* 2020;12(10):3113.

60. Tao R, Karliner JS, Simonis U, et al. Pyrroloquinoline quinone preserves mitochondrial function and prevents oxidative injury in adult rat cardiac myocytes. *Biochem Biophys Research Communications*. 2007;363(2):257–262.

61. Chowanadisai W, Bauerly KA, Tchaparian E, et al. Pyrroloquinoline quinone stimulates mitochondrial biogenesis through cAMP response element-binding protein phosphorylation and increased PGC-1α expression. *J Biol Chem.* 2010;285(1):142–152.

62. Stites, T, Storms D, Bauerly K, et al. Pyrroloquinoline quinone modulates mitochondrial quantity and function in mice. *The Journal of Nutrition.* 2006;136(2):390–396.

63. Zhang, Y, Feustel PJ, Kimelberg HK. Neuroprotection by pyrroloquinoline quinone (PQQ) in reversible middle cerebral artery occlusion in the adult rat. *Brain Res*. 2006;1094(1):200–206.

64. Alkahtani, S, Alarifi S, Alkahtane AA, et al. Pyrroloquinoline quinone alleviates oxidative damage induced by high glucose in HepG2 cells. *Saudi J Biol Sci*. 2021;28(11):6127–6132.

65. Cammaerts MC, Cammaerts D. Comparative outlook over three *Myrmica* species' biotopes and foragers' know-how. *Biologia.* 2014;69(8):1051–1058.

66. Cammaerts MC, Cammaerts R. Non-numerical distance and size effects in an ant. *J Biol and Life Science*. 2020;11(2):13–35.

67. Cammaerts MC, Cammaerts R. Weber's law applied to the ants' visual perception. *J Biol and Life Science*. 2020;11(2):36–61.

68. Cammaerts MC, Cammaerts R. Ants'numerosity ability defined in nine studies. *J Biol and Life Science*. 2020;11(1):121–142.

69. Cammaerts MC, Cammaerts R. Summary of seven more studies on numerosity abilities in an ant, four of them relating to human competence. *J Biol and Life Science.* 2020;11 (2): 296–326.

70. Cammaerts MC, Cammaerts R. A synthesis of six recent studies on numerosity abilities in an ant. *J Biol and Life Sciences*. 2022;13(1):1–23.

71. Cammaerts MC. Physiological and ethological effects of an herbicide largely used by non-professional persons; a study on ants as biological models. *RRJEAES*. 2022;10(06):1–20.

72. Cammaerts MC. Adverse effects of imodium (loperamide), the most used drug for treating diarrhea, examined on ants as biological models. *W J Pharm and Pharmaceut Sci*. 2022;11(9):1174–1196.

73. Cammaerts MC. Side effects of tetrazepam, a myorelaxant drug. *W J Pharm Pharmaceut Sciences*. 2022;11(10):67–91.

74. Cammaerts MC. Side effects of the antiemetic drug Motilium (domperidone) studied on ants as models. *AS Pharmacology.* 2022;3(11):9–23.

75. Cammaerts MC. Side effects of Cognizing, a dietary supplement used to improve the brain functioning, the active substance of which, citicoline, allows treating cerebral disorders, examined on ants as models. *EC Nutrition*. 2022;17(10):29–46.

76. Cammaerts MC. Side effects of the dietary supplement PQQ studied on ants as models. *EC Nutrition*. 2022;17(12):34–51.

77. Akel T, Bekheit S. Loperamide cardiotoxicity: a brief review *Ann Noninvasive Electrocardiol.* 2017;23(2):e12505.

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