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August 21, 2018

Foreign Affairs, Defence and Trade Committee
Department of the Senate
PO Box 6100
Parliament House
Canberra, Australian Capital Territory 2600

**Sent electronically**

**Re: Response to Inquiry Submissions**

Dear Committee Members,

The Quinism Foundation has been invited to respond to several submissions made to the Senate Foreign Affairs, Defence and Trade Committee Inquiry on the Use of the Quinoline Anti-Malarial Drugs Mefloquine and Tafenoquine in the Australian Defence Force. These include the submission of Mr. Mark Reid, dated July 28, 2018.

For brevity, this response focuses only on certain errors of fact that appear in this submission.

Our non-response to other statements in this submission, and our non-response to certain other submissions published by the Committee to date should not be construed as our agreement with these.

Indeed, our review of the submissions published by the Committee to date further underscores our belief that a Royal Commission is needed to fully investigate several issues related to the terms of reference.

We thank you in advance for your careful attention to the issues in our response.

Sincerely,

Remington Nevin, MD, MPH, DrPH
Executive Director, The Quinism Foundation

Enclosure: as described

**Response of The Quinism Foundation to the Submission of Mr. Mark Reid, dated July 28, 2018, to the Australian Senate Foreign Affairs, Defence and Trade References Committee's Inquiry into the Use of the Quinoline Anti-Malarial Drugs Mefloquine and Tafenoquine in the Australian Defence Force (ADF)**

The Quinism Foundation was invited to respond to the submission of Mr. Mark Reid on the basis of several statements therein, including one challenging the expertise and probity of the foundation's executive director, Dr. Nevin, who Mr. Reid claimed had "routinely misquoted scientific research conducted in the 1940s and 1950s", "by claiming all 8-aminoquinolines are neurotoxic" (p7).

In fact, the available evidence clearly supports a statement that all 8-aminoquinolines that have been appropriately tested have been proven to be neurotoxic. Dr. Schmidt, who was responsible for much of the U.S. government's testing of 8-aminoquinolines during the World War II-era and subsequent drug development programs, very clearly wrote in 1951 that "all of nearly one hundred and forty 8-aminoquinolines examined in this laboratory… produce rather remarkable and highly specific lesions in the central nervous system"[1]. The 1983 manuscript by Dr. Schmidt cited by Mr. Reid[2], which further describes the neurotoxicity of the 8-aminoquinoline class, reflects Dr. Schmidt's further experience with several additional compounds of the class that had been synthesized in the years since the WWII era.

Contrary to the claims of Mr. Reid that tafenoquine "is [a] 4-methyl substituted drug and would not be expected to [be] neurotoxic in Rhesus monkeys or humans", in the cited paper, Dr. Schmidt in fact never claims that 4-methyl substituted 8-aminoquinolines would not be neurotoxic. Indeed, of the drugs studied by Dr. Schmidt during the WWII-era program, several 4-methyl substituted drugs, including SN 13,623 and 14,011[3(p126)], are listed. Both SN 13,623 and 14,011 were each described as causing a pamaquine-like reaction in rhesus monkey. Although neurological reactions to pamaquine observed in rhesus monkeys had been once characterized by Dr. Schmidt as reversible[4], pamaquine was later found to produce strikingly similar effects to those observed later in man[5], causing swelling and subtle degeneration in scattered neurons throughout various brainstem nuclei including within the vestibular, supraspinal, ruber, ambiguus, dorsal motor, lateral cuneate, and lateral reticular nuclei, as well as the nuclei of cranial nerves III, IV, and VI[6].

Although Mr. Reid is therefore clearly incorrect in his claim that 4-methyl substituted 8-aminoquinolines lack neurotoxicity, what Mr. Reid may have been alluding to was Dr. Schmidt's finding in his paper that two particular 4-methyl substituted 8-aminoquinolines, which were structurally closely related to the highly neurotoxic drug plasmocid, "did not evoke symptoms of neuronal damage". This was apparently surprising to Dr. Schmidt, as he noted that plasmocid "evoked a syndrome attributable to destructive lesions in the spinal cord, brain stem, diencephalon, and corpus striatum" when tested in Rhesus monkey, and that "neurologic reactions, doubtless similar to these in origin, occurred in human subjects after administration of the compound"[2].

In this respect, it is important to note that Dr. Schmidt was merely commenting on the lack of outward symptoms produced with testing of these particular 4-methyl substituted 8-aminoquinolines in rhesus monkey but was not ruling out later neurohistopathological evidence of brainstem injury. Indeed, in an earlier paper, Dr. Schmidt had noted that other members of the 8-aminoquinoline class, including pamaquine, "did not evoke similar symptoms", but given "their high inherent toxicity and capacity to evoke reactions which might mask symptoms of low grade neuronal injury, plus the likelihood of their widespread use in malaria therapy made a detailed search for central nervous system lesions highly desirable"[1]. In other words, Dr. Schmidt was alluding to the need for definitive neurohistopathological testing of drugs of this class, even in the absence of outward symptoms.

In his paper, Dr. Schmidt had speculated that "methyl substitution at position 4 abolishes the prohibitive neurotoxicity characteristic of 6-methoxy-8-aminoquinolines", in certain drugs, "with

terminal alkylamino or dialkylamino substituents and with chains two to three carbons in length between the 8- and terminal amino groups". However, the only support for this statement was a claim by Dr. Schmidt, cited by Mr. Reid, that "results of toxicity studies on five pairs of compounds which showed that the 6-methody members of the pairs evoked the aforementioned symptoms, whereas the 4-methyl-6-methoxy members did not". This particular statement was again merely commenting on the lack of outward symptoms produced with testing of these particular 4-methyl substituted 8-aminoquinolines. Nowhere in the paper by Dr. Schmidt was this statement ever subjected to confirmatory proof through subsequent neurohistopathological testing, and a claimed "manuscript in preparation" on this was never ultimately published. This leads to a reasonable conclusion that this claim was later disproven.

Given that this tenuous claim appears to be the only published basis for the U.S. military and the ADF proceeding with the development and clinical testing of tafenoquine given the inherent neurotoxicity of closely related members of the 8-aminoquinoline class, the lack of definitive neurohistopathological testing of tafenoquine should be considered deeply problematic. Indeed, when subjected to definitive neurohistopathological testing in rhesus monkey, all antimalarial drugs of the 8-aminoquinoline class for which published and publicly-available evidence are available have been proven to induce lesions in the central nervous system. When administered clinically, the signs and symptoms produced by these drugs reflect the localization of these lesions. This very property is why several previously-deployed drugs of this class, including plasmocid and pamaquine, have been withdrawn from widespread clinical use.

Even primaquine, alone among the deployed 8-aminoquinolines in not being withdrawn, has been found to share the neurotoxicity of other members of the 8-aminoquinoline class. Although primaquine has been claimed by Mr. Reid to be safe, primaquine has never undergone randomized blinded testing of its neuropsychiatric safety. Indeed, since the drug's widespread deployment, since primaquine is very seldomly administered alone, any neuropsychiatric adverse effects from primaquine may have been simply misattributed to chloroquine or to mefloquine, which have been ubiquitously co-administered, or to the effects of malaria itself. Such simple misattribution may most parsimoniously explain the seemingly discrepancy between primaquine's seemingly benign post-marketing profile, and the incontrovertible evidence of its CNS toxicity. As noted by Dr. Schmidt, "effects on the central nervous system of the rhesus monkey of the newer antimalarial drugs pentaquine, isopentaquine, and primaquine", "were generally similar [to the effects of pamaquine] in that the principal lesions were produced in the dorsal motor, supraoptic and paraventricular nuclei, and in a small group of cells associated with Meynert's commissure [i.e. the dorsal supraoptic commissure]". In addition to these areas, Dr. Schmidt found that on neurohistopathological testing in rhesus monkey, primaquine also induced injury to the nucleus ruber, the oculogyric nuclei, and to the cuneate, hypoglossal, vestibular, and the mesencephalic V nucleus[1].

Although various arguments have been raised by Mr. Reid as to why tafenoquine, alone among the deployed 8-aminoquinolines, should be spared published and publicly-available neurohistopathological testing in Rhesus monkey, these arguments are ultimately unsatisfying, and suggest a failure to learn from the lessons of recent history. For example, had mefloquine been subjected to definitive rhesus monkey testing at the time of its development, the drug's clinically significant neurotoxicity, which is acknowledged even by the drug's sponsor[7], would likely have been immediately recognized, rather than being recognized only several decades later, and only after the drug's widespread clinical use.

In this respect, it is telling, that, as did proponents of mefloquine when this drug was first brought to market, Mr. Reid has also claimed that there is *"*no evidence that tafenoquine has a neuropsychiatric liability" (p2).

This statement is clearly erroneous at face value. The U.S. Food and Drug Administration requires that the newly-approved U.S. tafenoquine drug label (for Arakoda™) carry the following warnings for clinicians, informing of the neuropsychiatric liability of the drug:

- That tafenoquine is contraindicated in "patients with a history of psychotic disorders or current psychotic symptoms (i.e. hallucinations, delusions, and/or grossly disorganized behavior)". If these symptoms occur, clinicians should "consider discontinuation", and "prompt evaluation by a mental health professional as soon as possible".

- That patients taking tafenoquine be "promptly evaluated by a medical professional" if "[o]ther psychiatric symptoms" occur, "such as" (but presumably not limited to) "changes in mood, anxiety, insomnia, and nightmares", "if they are moderate and last more than three days or are severe".

Similarly, the newly-approved U.S. tafenoquine drug label (for Arakoda™) instructs clinicians to advise patients who experience "confused thinking" while taking tafenoquine "to seek medical attention as soon as possible". FDA has also required that the newly-approved U.S. tafenoquine medication guide (for Arakoda™) include the following patient guidance:

- That the most common side effects of tafenoquine include "dizziness… insomnia, depression, abnormal dreams and anxiety".

- That patients call their healthcare provider if they develop these side effects "for 3 days or longer" while taking tafenoquine.

- That psychiatric symptoms may not happen right away.

It is the position of The Quinism Foundation that, as with mefloquine, any psychiatric symptoms that develop while taking tafenoquine for the prevention of malaria, including those as seemingly mild as insomnia or abnormal dreams, must themselves be considered serious adverse reactions[8], and prodromal to other more serious adverse effects and thus require the drug's immediate discontinuation. This position appears to be echoed in the FDA's warnings for tafenoquine, which suggest a need to discontinue the drug should such seemingly mild symptoms as "insomnia" or "abnormal dreams" continue "for 3 days or longer" while taking the drug or be "severe".

Particularly given the seeming denial of these effects by many members of the malariology and drug development communities, including Mr. Reid, and their apparent willingness to attribute such effects to any and all causes other than the drug, the Quinism Foundation recently wrote to the Director of the U.S. Centers for Disease Control (CDC), expressing concern that FDA's warnings may be overlooked — or even trivialized — by travel medicine practitioners, as FDA's warnings for mefloquine once were, unless this advice is properly emphasized in CDC's prescribing guidance and recommendations, including the CDC's Yellow Book.

The foundation noted in this respect that the FDA-approved U.S. label for mefloquine had warned since 2002 of the need to discontinue the drug at the onset of such psychiatric symptoms[9], but absent appropriate and timely emphasis in the CDC's Yellow Book, and given a similar seeming denial of these effects by members of the malariology and drug development communities, such warnings had to be eventually elevated by FDA to inclusion in a boxed warning.

Its correspondence, the Quinism Foundation therefore requested that CDC's prescribing guidance and recommendations, including in the CDC's Yellow Book, do the following with respect to tafenoquine:

- Recommend that prescribers schedule a visit with the patient prior to travel, to assess for the development of psychiatric symptoms following administration of the tafenoquine loading dose, recognizing that access to healthcare, as recommended in the FDA-approved U.S. tafenoquine drug label, may be limited once travel begins.

- Recommend that tafenoquine should not be prescribed prior to sleep-disrupting travel across time zones, to which insomnia as a side effect of tafenoquine may be misattributed, and that tafenoquine should not be prescribed with hypnotics or other sleep-aids, which may confound recognition of insomnia as a side effect of tafenoquine.

- Recommend that tafenoquine should not be prescribed prior to military deployments and other high-stress travel, including travel for humanitarian emergencies and disaster response, to which psychiatric side effects of tafenoquine, including changes in mood, anxiety, abnormal dreams or nightmares, may risk being misattributed.

- Recommend that tafenoquine should not be prescribed for travelers with existing psychiatric symptoms or disorders, to which other psychiatric side effects of tafenoquine may similarly risk being misattributed.

**References**

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2. Schmidt LH. Relationships between chemical structures of 8-aminoquinolines and their capacities for radical cure of infections with Plasmodium cynomolgi in rhesus monkeys. *Antimicrobial Agents and Chemotherapy*. 1983;24(5):615-652.
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