CONCLUSIONS

SUFFICIENT EVIDENCE OF AN ASSOCIATION

Epidemiologic evidence is sufficient to conclude that there is a positive association between the prophylactic use of an antimalarial drug and the outcome in studies in which chance, bias, and confounding can be ruled out with reasonable confidence. For example, if several small studies without known bias and confounding show an association that is consistent in magnitude and direction, there could be sufficient evidence of an association. Experimental data supporting biologic plausibility strengthen the evidence of an association but are not a prerequisite and are not enough to establish an association without corresponding epidemiologic findings. There is sufficient evidence of an association between the following antimalarial drugs and health outcomes:

- Tafenoquine and vortex keratopathy

LIMITED OR SUGGESTIVE EVIDENCE OF AN ASSOCIATION

Epidemiologic evidence suggests an association between prophylactic use of an antimalarial drug of interest and the outcome in studies of humans, but the evidence can be limited by an inability to confidently rule out chance, bias, or confounding. For example, a high-quality study with strong findings of a positive association in conjunction with less compelling or inconsistent results from studies of populations with similar exposures could constitute such evidence. None of the associations between antimalarial drugs and health outcomes were determined to constitute limited or suggestive evidence.

INADEQUATE OR INSUFFICIENT EVIDENCE OF AN ASSOCIATION

The available epidemiologic studies are of insufficient quality, validity, consistency, or statistical power to support a conclusion regarding the presence or absence of an association. For example, such studies may have failed to control for confounding factors or had inadequate assessment of exposure or outcomes. Because the committee could not possibly address every rare condition or disease, it does not draw explicit conclusions about outcomes that are not discussed, and instead it makes conclusions by body system. It also notes whether the existing evidence, including use of nonepidemiologic information, merits additional research in a specific area. There is inadequate or insufficient evidence of an association between the following antimalarial drugs and health outcomes, grouped by whether the existing empirical evidence supports additional research:

Empirical basis for additional research:

- Mefloquine and neurologic events
- Mefloquine and psychiatric events, including PTSD
- Mefloquine and eye disorders, including cataract
- Tafenoquine and psychiatric events
- Tafenoquine and eye disorders (other than vortex keratopathy)
- Atovaquone/Proguanil and eye disorders
- Doxycycline and gastrointestinal events

INADEQUATE OR INSUFFICIENT EVIDENCE OF AN ASSOCIATION (CONTINUED)

No empirical basis for additional research

- Mefloquine and gastrointestinal events
- Mefloquine and cardiovascular events
- Tafenoquine and neurologic events
- Tafenoquine and gastrointestinal events
- Tafenoquine and cardiovascular events
- Atovaquone/Proguanil and neurologic events
- Atovaquone/Proguanil and psychiatric events
- Atovaquone/Proguanil and gastrointestinal events
- Atovaquone/Proguanil and cardiovascular events
- Doxycycline and neurologic events
- Doxycycline and psychiatric events
- Doxycycline and eye disorders
- Doxycycline and cardiovascular events
- Primaquine and neurologic events
- Primaquine and psychiatric events
- Primaquine and gastrointestinal events
- Primaquine and eye disorders
- Primaquine and cardiovascular events
- Chloroquine and neurologic events
- Chloroquine and psychiatric events
- Chloroquine and gastrointestinal events
- Chloroquine and eye disorders
- Chloroquine and cardiovascular events

LIMITED OR SUGGESTIVE EVIDENCE OF NO ASSOCIATION

Several adequate studies, which cover the full range of human exposure are consistent in showing no association or reduced risk (not distinguished for the purposes of this evaluation which was focused on the potential for adverse effects) with an exposure to an antimalarial drug of interest at any concentration and had relatively narrow confidence intervals. A conclusion of "no association" is inevitably limited to the conditions, exposures, and observation periods covered by the available studies, and the possibility of a small increase in risk related to the magnitude of exposure studied can never be excluded. However, a change in classification from inadequate or insufficient evidence of an association to limited or suggestive evidence of no association would require new studies that correct for the methodologic problems of previous studies and that have samples large enough to limit the possible study results attributable to chance. None of the associations between the antimalarial drugs and health outcomes were determined to constitute limited or suggestive evidence of no association.

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