Comments about the epidemiological evidence presented by ANVISA that Parkinson’s Disease is associated with exposure to paraquat.

The epidemiological evidence presented by ANVISA that Parkinson’s Disease (PD) is associated with exposure to paraquat is largely based on a literature review of epidemiological studies linking exposure to pesticides and health effects conducted by Ntzani et al (2013) for EFSA. Ntzani et al (2013) state that they identified 9 studies which assessed the association between paraquat exposure and PD, and the results of these studies were included in a meta-analysis, although Figure 30 shows that results were included from only 8 studies (all case-control studies). Two odds ratios (OR) were included from one study (Costello et al, 2009; labelled as NRD 020): odds ratios for exposure to paraquat only, and exposure to both paraquat and maneb. However, the literature search of Ntzani et al (2013) missed two of the most informative studies by Tomenson et al (2011) and Elbaz et al (2009). Both studies provide no evidence of an association between PD and exposure to paraquat. In addition, the meta-analyses included in the report by Ntzani et al (2013) are little more than a statistical pooling of results. Ntzani et al (2013) did not assess the quality of the studies included in their analysis and many have obvious methodological limitations, especially the assessment of exposure to paraquat (see Mandel et al, 2012), and Ntzani et al (2013) did not investigate reasons for heterogeneity of findings.

The studies by Tomenson et al (2011) and Elbaz et al (2009) are clearly relevant. Tomenson et al (2011) is a cohort study of mortality among a UK workforce (926 male and 42 female workers) who manufactured paraquat between 1961 and 1995 and who were followed through 30 June 2009 by which time 307 deaths had occurred. The study provided no evidence of an increased risk of PD, or increased mortalities from other causes. One male death was due to PD, but no other death certificates mentioned PD. At least 3.3 death certificates of male employees would have been expected to have mentioned PD (standardised mortality ratio=0.31; 95% CI 0.01 to 1.71). A limitation of the study is that only information from death certificates of deceased workers was available, and it was not possible to study the morbidity of the entire group. It is widely regarded that most patients with PD die of its complications and not the disease, and consequently mortality studies of PD have little value. However, the information available suggests that PD is coded as the underlying cause of death of more than a third of UK PD patients, and it is mentioned on the death certificates of approximately three quarters of UK patients (Phillips et al, 1999).

Studies from Scandinavia and the USA have generally reported slightly lower instances of PD being a mentioned cause of death for individuals with PD. A major strength of the study is that exposure of the cohort of paraquat production workers was confirmed by comprehensive job histories and the availability of personal monitoring information. This was not the case for any of the case-control studies listed by Ntzani et al (2013) which relied on self-reported exposure information, or presumed exposure because of proximity of residence, workplace or private well to areas where paraquat had been applied (potentially more than 2 km distant). Furthermore, Tomenson et al (2011) reported that personal monitoring results indicated that the exposure of these paraquat production workers on a daily basis was at least comparable with that of a paraquat sprayer or mixer/loader. However, workers engaged in
paraquat production had the potential to be exposed daily, whereas workers employed as sprayers are unlikely to have sprayed paraquat on a daily basis, and many subjects described as paraquat users in case-control studies may have used paraquat on an occasional basis only.

Elbaz et al (2009) performed a large case-control study which included 224 PD cases from the Mutualite Sociale Agricole (France) that were matched to 557 controls free of PD and affiliated with the same health insurance. A comprehensive assessment of exposure to pesticides was performed and analyses of the relation between PD and professional exposure to pesticides were performed for 29 pesticide families including paraquat (quaternary ammonium herbicide), and data were analyzed both using a complete-case and an imputed dataset (multiple imputation was used to impute missing values for pesticide families). There was no evidence of an association between paraquat exposure and PD with an OR of 1.1 (95% CI 0.6, 2.0) based on complete cases, and 1.2 (95% CI 0.7, 2.1) based on imputed data.

Ntzani et al (2013) state that “the observed effect indicated a statistically significant association between paraquat exposure and PD with the presence of moderate heterogeneity (random-effects OR=1.32, 95% CI=1.10–1.60, I²=34%) (Figure 30)”.

Conclusion
The epidemiological evidence presented by ANVISA that Parkinson’s Disease is associated with exposure to paraquat is heavily based on a report by Ntzani et al (2013) which contains several errors, including the exclusion of findings from two very relevant studies (Tomenson et al, 2011; Elbaz et al, 2009) and the use of random effects analysis, which is more appropriate given the wide variation in exposure levels (from ambient residential levels up to occupational exposures). It is unclear whether the more appropriate random effects analysis would also have indicated a significant association. Certainly, the pooled odds ratio will be reduced if results from Elbaz et al (2009) and Tomenson et al (2011) are included in the analysis.
et al, 2011; Elbaz et al, 2009). A more thorough review of the epidemiological evidence provides little support for the conclusion by ANVISA that much of the epidemiology relating to PD and paraquat exposure was well conducted and has consistent findings, although ANVISA does acknowledge that some studies have limitations (confounding factors and evaluation methodology).

References


Ntzani EE, Chondrogiorgi M, Ntritsos G, Evangelou E, Tzoulaki I. Literature review on epidemiological studies linking exposure to pesticides and health effects. EFSA supporting publication 2013;EN-497.

