Illuminating the Environmental Photodegradation of Valium and its Human Metabolites

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Background

- In recent years the occurrence, fate and effects of pharmaceutically active compounds (PhACs) in the environment has been recognised as an emerging issue.
- Since PhACs are developed with the intention of performing a biological action, these findings have prompted concern over their environmental fate and potential ecological effects.
- Photochemical degradation is potentially a very important degradation mechanism for the removal of PhACs in the aquatic environment.
- Many PhACs feature aromatic rings, heteroatoms, or other functional groups that can either absorb solar radiation or react with photogenerated transient species in natural waters (e.g. reactive oxygen species and photoexcited natural organic matter).
- A comprehensive search of the literature, involving research into around 200 PhACs previously detected in the environment was undertaken to establish the most suitable candidates for photodegradation studies.
- The anti-anxiety drug diazepam (Valium®) along with its known human metabolites, nordiazepam, temazepam and oxazepam were selected for photodegradation studies (Figure 1).

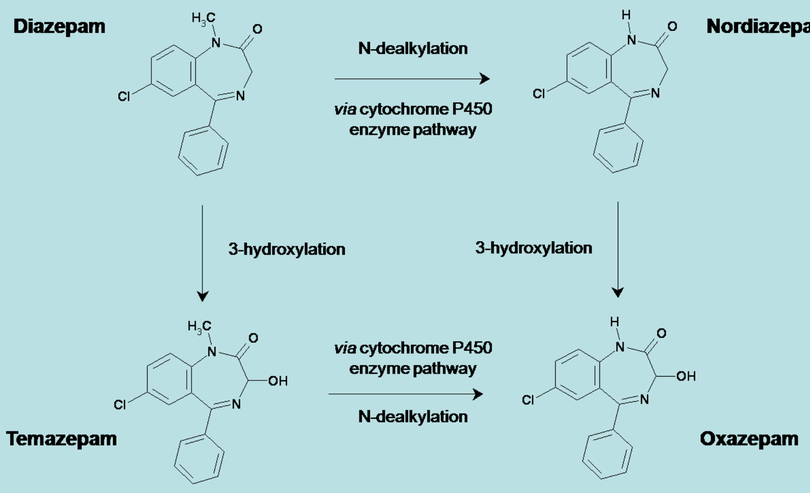

Figure 1. Metabolism of diazepam (Valium®) in the human body

Methods

Samples

- Solutions (1 μg mL^{-1}) of each PhAC were prepared in distilled water and in humic acid containing natural waters respectively. Aliquots were added to quartz photolysis tubes, each with a sample volume of 50 mL. Tubes containing control samples were wrapped in aluminium foil.

Irradiation

- Apparatus - 1.8 KW Xenon Arc lamp fitted with a quartz glass filter with a UV cut-off at 290 nm (Heraeus Suntest CPS Instrument).

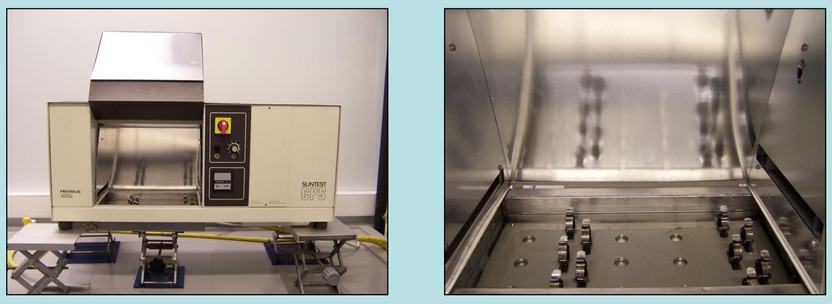

Figure 2. Heraeus Suntest CPS Xenon Arc lamp.

- Samples were placed in a bath of glycerol which was maintained at constant temperature by circulating coolant from a chiller unit through a reservoir surrounding the tank. A data logger was used to continually monitor the cooling bath temperature.
- Aliquots were taken after various periods of irradiation and spiked with internal standard (oxazepam-d_5, 1 μg mL^{-1}). Solid phase extraction (SPE) was carried out using Strata™-X SPE cartridges (500mg polymeric sorbent x 3 mL, Phenomenex, Macclesfield, UK). Each sample was transferred to a 7ml vial, wrapped in foil and refrigerated until required.

Analysis

- Reverse phase liquid chromatography (RP-LC) separation method (C^{18} column, Gradient program).
- Finnigan Mat LCQ™ ion trap mass spectrometer (ThermoFinnigan, San Jose, CA, USA) with an electrospray ionisation (ESI) interface.

Results

- The decline in concentration for each PhAC with increasing irradiation time for each experiment followed first order kinetics. Photodegradation rate constants (k_p) and environmental half lives ($t_{1/2}$) were determined (Figure 3).
- Photodegradation products were detected in LC/ESI-MS extracted ion chromatograms (EIC) of irradiated samples (Figure 3). ESI-MS^n spectra were obtained for each photoproduct and structures were proposed (Figure 4). Identification was aided by comparison with authentic compounds where available.

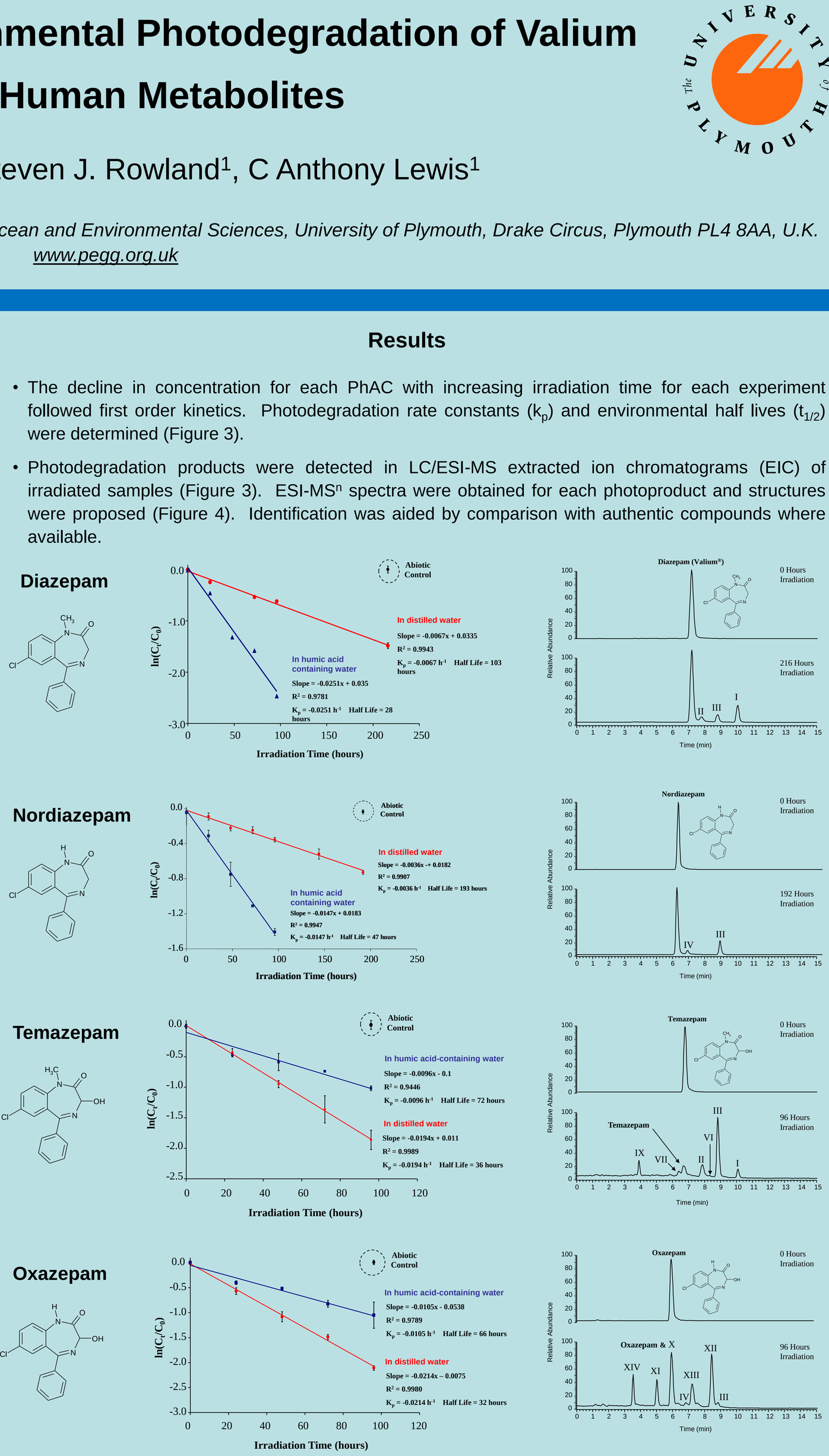

Figure 3. First order photodegradation rate constants (k_p) and half lives ($t_{1/2}$) for selected PhACs. Comparison of LC/ESI-MS (EIC) chromatograms for selected PhACs at the beginning and end of irradiation experiments.

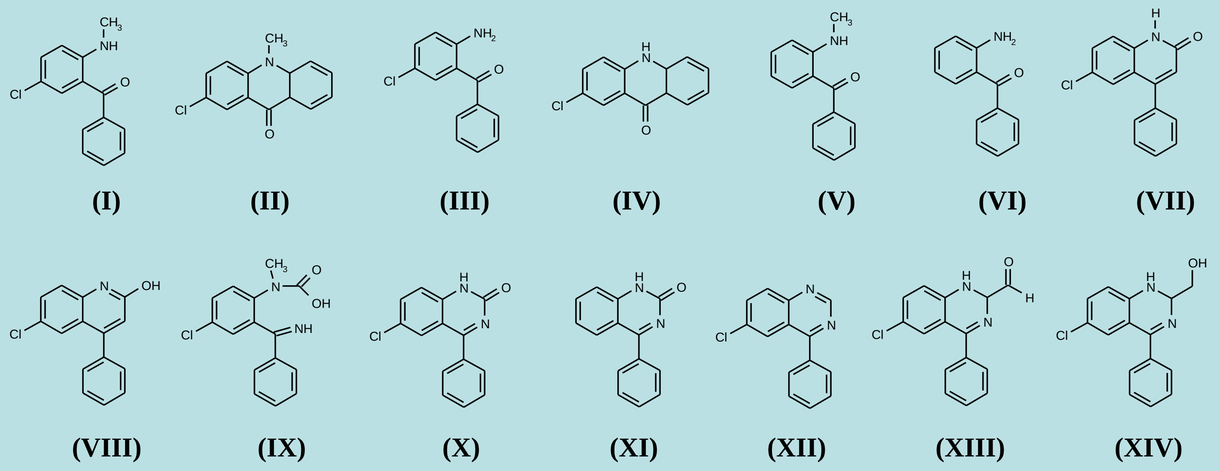

Figure 4. Photoproducts identified from the irradiation of diazepam and its human metabolites in aqueous solutions

Conclusions

The results demonstrate that with photolysis half-lives ranging from 193-32 hours, diazepam and its human metabolites are unlikely to be persistent in natural waters. Photodegradation products have been successfully identified using elrctrospray ionisation mulit-stage mass spectrometry (ESI-MS^n).

Acknowledgements

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