A Risk Assessment Framework for Antimicrobial Resistance Development
Associated with the Use of Microbicides in Home and Personal Care Products

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Introduction

Responsible evaluation and development of new microbial systems needs to consider the risk of microbial resistance developing during use, particularly where clinically-relevant cross-resistance to antibiotics might emerge. There are currently no risk assessment frameworks available for this purpose, resulting in lack of consistency of data interpretation from susceptibility studies, and ultimately on decisions relating to safety. We have therefore developed a risk assessment framework and validated it with a number of case studies.

Methods

• The risk assessment framework consists of three tiers (Fig. 1) of increasing experimental data demands. The end-point of the framework is an estimate of the likelihood of resistance development (i.e. microbicide resistance and cross-resistance to clinically-relevant antimicrobials) following use of home and personal care (HPC) products containing microbicides.

Fig. 1 Tiered approach to AMR Risk Assessment

• The starting point is an evidence-weighted model for assessment of candidate agents addressing realistic exposure (in-use) conditions (Tier 0) using existing data from literature.

• When no sufficient evidence is available in literature, the framework progresses through laboratory evaluation (Tier 1). This is based on an experimental protocol (Knapp et al., 2015) created to assess changes in susceptibility (including cross-resistance), following realistic exposures to formulations or actives of interest.

• If Tier 1 shows potential for resistance development, mechanisms of resistance could be investigated further (Tier 2).

Tier 0 assessment:

• Using Tier 0, there was enough evidence from the literature to conclude that a hand soap bar containing a proprietary blend of Thymol, Terpinene and Silver oxide was low risk from an AMR perspective.

• Tier 0 uses a Weight of Evidence (WoE) approach to evaluate risk (Fig. 2) on the basis of existing evidence (i.e. scientific literature or information resulting from internal reports/studies).

• The WoE approach is based on heuristic rules to support decision-making, and demands that a reasonable body of evidence is available. It considers the principal risk-contributing factors, the connections or relations between those factors, and attributes weights or scores to those factors on the basis of their relative contribution to risk. The heuristic rules have been structured into a model which aims at ensuring consistency among risk assessors in Unilever (Fig. 2).

• This systematic approach was developed with inputs from a workshop involving experts in microbicides, antimicrobial resistance (AMR) and risk assessment for identification of risk-contributing factors (Maillard et al., 2013).

• For the hand soap bar assessment, 58 peer-reviewed publications were used to gather the evidence for the three microbicides of interest.

Table 1. Formulation and test conditions used for Tier 1 assessment.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Test Microorganism</th>
<th>Test Conditions</th>
<th>MIC (µg/mL)</th>
<th>MBC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAC in aqueous solution</td>
<td>P. aeruginosa (ATCC 15442)</td>
<td>0.075 %*, 15 min</td>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.006 %*, 15 min</td>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.008 %*, 15 min</td>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01 %*, 15 min</td>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.004 %, 15 min</td>
<td>0.6</td>
<td>1</td>
</tr>
</tbody>
</table>

Results

Tier 1 assessment:

• The remaining 5 formulations were taken through to Tier 1, resulting in limited changes in microbicide susceptibility after realistic exposures tested on a broad range of bacteria (asplanktonic – single & repeated exposures–, biofilm and desiccated cells). There was no development of clinical resistance to any of the antibiotics tested (using EUCAST breakpoints).

• Results showed that Tier 2 data were not needed for risk assessment.

• Here we present results for 1 of the 5 formulations (Table 1, Figs. 3 and 4).

• Planktonic assessment: no survivors following exposure.

• Biofilm assessment: strains in bold (Table 1) survived exposure. Results shown in Figs. 3 and 4.

Fig. 3 Tier 1 Assessment – in Formulation

Fig. 4 Tier 1 Assessment – Active alone

Conclusions

• Our studies showed that the 6 formulations evaluated were low risk in terms of microbial resistance development and cross-resistance to antibiotics.

• The AMR risk assessment framework gives an approach/methodology which ensures that personal/home care products containing antimicrobial actives are safe by design with regard to resistance and cross resistance risks.

References