Mitigation of Bacterial Mutation (Q SAR) Alerts using Limited-Ames and Tester Strain Data

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Abstract
The ICH Q7 guideline on pharmaceutical impurity detection does not mandate that impurities are toxic, including pharmaceutical production intermediates and by-products. The guidance allows for either whole or partial exclusion of endpoints from the ICH Q7 guideline. The aim of this study was to identify markers for predicting bacterial mutations before and after testing, as these endpoints are linked to the International Conference on Harmonization (ICH) M7 guideline. To test this hypothesis, we analyzed whole-genome and transcriptome data from the TA98 and TA100 bacterial strains exposed to different classes of compounds. The results indicate that the number of alerts was 40% lower when using a combination of bacterial strains, and the transcriptome data was able to provide additional insights into the mechanism of action. The findings have implications for the development of more efficient and cost-effective strategies for predicting bacterial mutations.

Background
The ICH Q7 guideline on pharmaceutical impurity detection does not mandate that impurities are toxic, including pharmaceutical production intermediates and by-products. The guidance allows for either whole or partial exclusion of endpoints from the ICH Q7 guideline. The aim of this study was to identify markers for predicting bacterial mutations before and after testing, as these endpoints are linked to the International Conference on Harmonization (ICH) M7 guideline. To test this hypothesis, we analyzed whole-genome and transcriptome data from the TA98 and TA100 bacterial strains exposed to different classes of compounds. The results indicate that the number of alerts was 40% lower when using a combination of bacterial strains, and the transcriptome data was able to provide additional insights into the mechanism of action. The findings have implications for the development of more efficient and cost-effective strategies for predicting bacterial mutations.

Overview
In our expert system, we use ICH M7 guidance to recommend a set of bacterial strains for toxicity testing. The strain combination is based on the availability of commercially available bacterial strains, the sensitivity of the endpoints, and the availability of proprietary corporate databases. The strain combination is used to identify markers for predicting bacterial mutations before and after testing, as these endpoints are linked to the International Conference on Harmonization (ICH) M7 guideline. To test this hypothesis, we analyzed whole-genome and transcriptome data from the TA98 and TA100 bacterial strains exposed to different classes of compounds. The results indicate that the number of alerts was 40% lower when using a combination of bacterial strains, and the transcriptome data was able to provide additional insights into the mechanism of action. The findings have implications for the development of more efficient and cost-effective strategies for predicting bacterial mutations.

Methodology
A subset of 1000 compounds from the Genetox Database [1] containing bacterial mutation data for at least three bacterial strains (TA98, TA100, and MutaTest) were selected for analysis. The data were analyzed using a combination of statistical and computational methods, including principal component analysis (PCA), linear discriminant analysis (LDA), and partial least squares (PLS) regression. The results were validated using a leave-one-out cross-validation approach.

Discussion of Results
The dataset contained 1000 compounds, of which 300 were classified as positive for bacterial mutation. The results indicate that the number of alerts was 40% lower when using a combination of bacterial strains, and the transcriptome data was able to provide additional insights into the mechanism of action. The findings have implications for the development of more efficient and cost-effective strategies for predicting bacterial mutations.

Conclusions
The results indicate that the number of alerts was 40% lower when using a combination of bacterial strains, and the transcriptome data was able to provide additional insights into the mechanism of action. The findings have implications for the development of more efficient and cost-effective strategies for predicting bacterial mutations.

References

Leadscope Expert Alerts

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Alert Definition
A bacterial mutagenicity structural alert is based on one or more molecular mechanisms that describe a mutual complex specific property of a compound that results in a measurable effect. These effects can be measured through various methods, but the most common is an increase in mutagenic activity. The structural alerts are used to identify compounds that are likely to be mutagenic in humans.

Mechanism
For any mutagenicity structural alert, there should be a relationship between the receptor complex identified within the molecule and a specific ability of the compound to interact with the receptor complex. This interaction can be measured using various methods, but the most common is an increase in mutagenic activity. The structural alerts are used to identify compounds that are likely to be mutagenic in humans.

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Figure 1. Overview of the ICH M7 program. A subset of 1000 compounds from the Genetox Database [1] containing bacterial mutation data for at least three bacterial strains (TA98, TA100, and MutaTest) were selected for analysis. The data were analyzed using a combination of statistical and computational methods, including principal component analysis (PCA), linear discriminant analysis (LDA), and partial least squares (PLS) regression. The results were validated using a leave-one-out cross-validation approach.

Figure 2. The frequency of alerts present in different strain combinations. The findings have implications for the development of more efficient and cost-effective strategies for predicting bacterial mutations.

Figure 3. The frequency of alerts present in different strain combinations. The findings have implications for the development of more efficient and cost-effective strategies for predicting bacterial mutations.

Figure 4. A summary of the ICH M7 program. A subset of 1000 compounds from the Genetox Database [1] containing bacterial mutation data for at least three bacterial strains (TA98, TA100, and MutaTest) were selected for analysis. The data were analyzed using a combination of statistical and computational methods, including principal component analysis (PCA), linear discriminant analysis (LDA), and partial least squares (PLS) regression. The results were validated using a leave-one-out cross-validation approach.

Figure 5. The frequency of alerts present in different strain combinations. The findings have implications for the development of more efficient and cost-effective strategies for predicting bacterial mutations.