Paper 206-27

Regulatory Review of Animal Carcinogenicity Studies Using SAS/IntrNet®

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ABSTRACT

This software tool, WebCarcin is created using SAS/IntrNet (v. 1.2, running Windows 95), to overcome the limitations of a currently used SAS/AF application, Carcin[1] in the regulatory review of animal carcinogenicity at FDA. With the help of this tool, statisticians can coordinate review strategies with reviewing pharmacologists, analyze sponsor-submitted data, and share statistical results with the review team. This tool, with its data-managing capabilities, significantly reduces time and efforts in data manipulations, hence improving the efficiency of the regulatory review.

INTRODUCTION

An important area of regulatory review of INDs and NDAs at FDA is the analysis of animal-carcinogenicity data submitted by drug sponsors. Not only do the FDA's statisticians require that the data from sponsors be clearly documented and accurate, but they also need a user-friendly analytical tool to evaluate and analyze the data. Reviewers in other disciplines are increasingly acquiring more data-exploratory and analytical tools to meet their review needs. People need software tools allowing real-time data analysis and data/results sharing--leading to intelligent, timely decision-making.

We, as FDA's statisticians and also as new software developers and creators of the web site, http://eReview/Nda shown above, aim to research, develop, and implement web-based review tools to facilitate reviewers in statistics, medicine, pharm-tox, chemistry, and other areas at FDA. These tools enable interested users to perform analyses online.

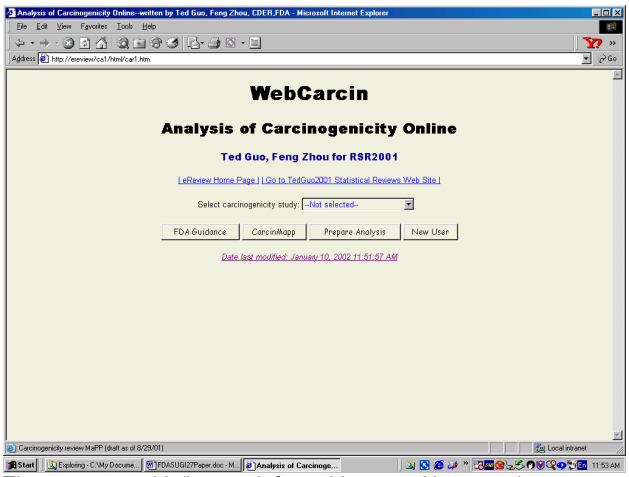
One such tool, WebCarcin, designed to evaluate and analyze sponsors' animal carcinogenicity studies has the features of

- Managing a centralized and standardized database for carcinogenicity study review
- Coordinating review strategies with reviewing pharmacologist
- Analyzing animal carcinogenicity data with flexible options

All the actions behind the scene are done by SAS programs programmed in Application Dispatcher or htmSQL.

[1] Carcin is a SAS/AF application is shared among statisticians at FDA internally. It was developed by FDA's statisticians.

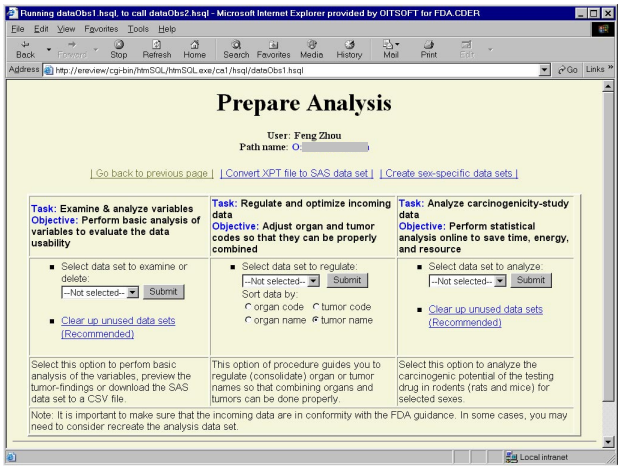
MANAGING DATA[1]



The user starts his/her work from this page. Here are the steps to start the review:

- New user must register to create a user's profile and obtain an access PIN# from us.
- We help control the data quality. Our jobs include
  - Evaluating the incoming data for quality and conformity with FDA guidance for electronic submission
  - Uploading acceptable data to the server
- We notify the user when the analysis data set is loaded and ready for use.

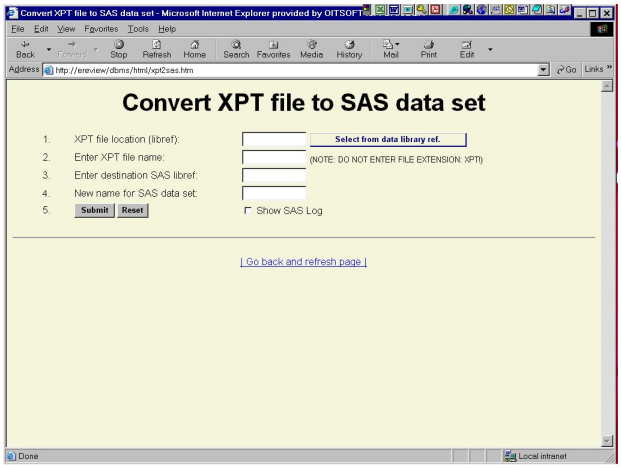
PREPARE ANALYSIS



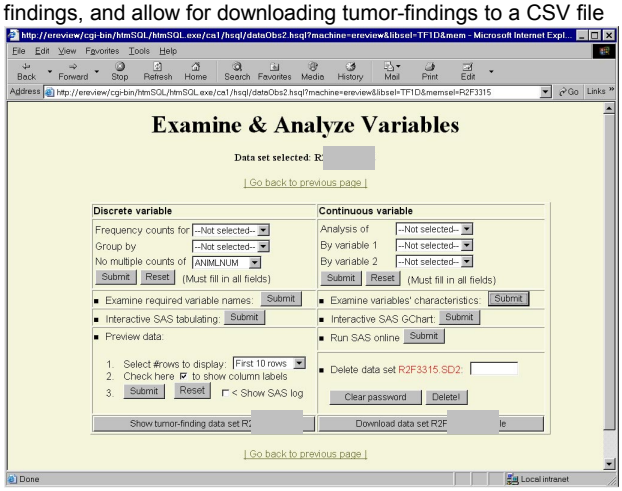
Having opened this page, the user may choose to perform one of the following tasks:

- Create analysis datasets.
- Examine & analyze variables.
- Regulate and optimize incoming data.
- Analyze animal carcinogenicity data.

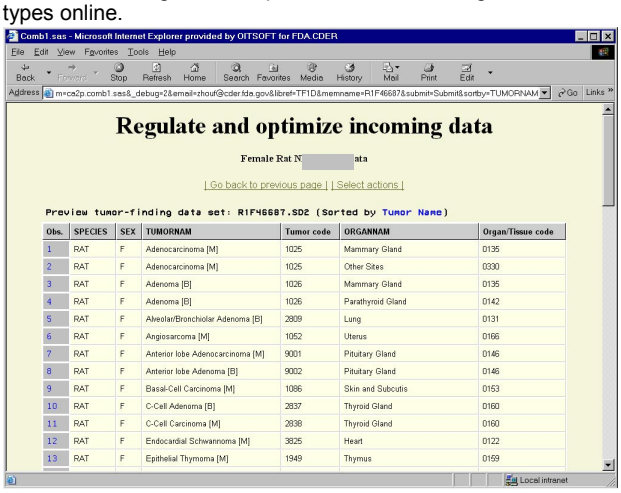
• **Create analysis datasets** – convert an incoming data set as an XPT file to a SAS data set and create gender-species specific data sets.



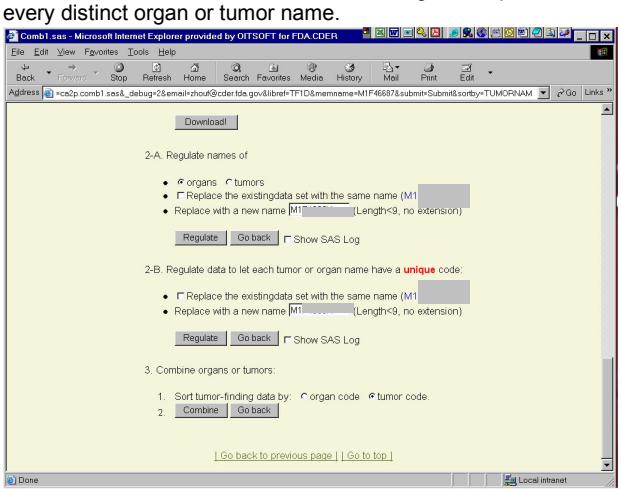
• **Examine & analyze variables** - perform basic analysis on the variables to evaluate the data usability, preview the tumor-findings, and allow for downloading tumor-findings to a CSV file



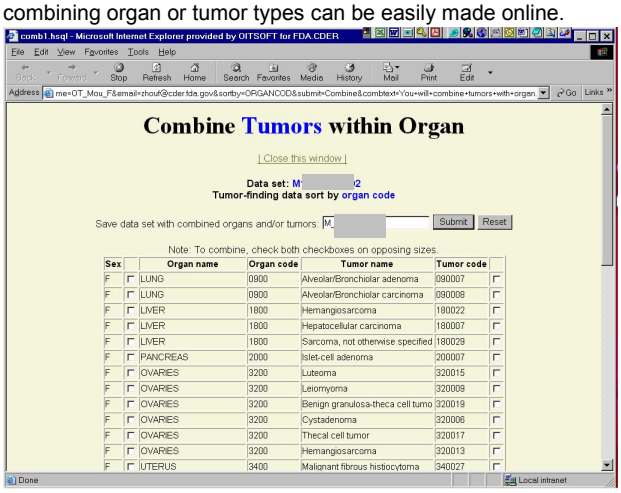
• **Regulate and optimize incoming data** - Repair organ and tumor names to have each organ or tumor have a unique name and regulate organ or tumor codes to have each organ or tumor have a unique code. Any organ or tumor having more than one code will be assigned a unique code. Combine organ or tumor types online.



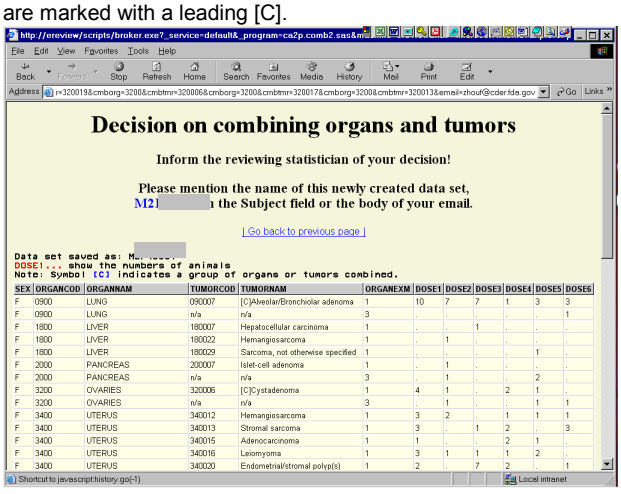
• **Regulate and optimize incoming data (cont'd)** – Select Action 2-A to regulate (fix and consolidate) misspecified organ and tumor names. Select Action 2-B to assign a unique code to every distinct organ or tumor name.



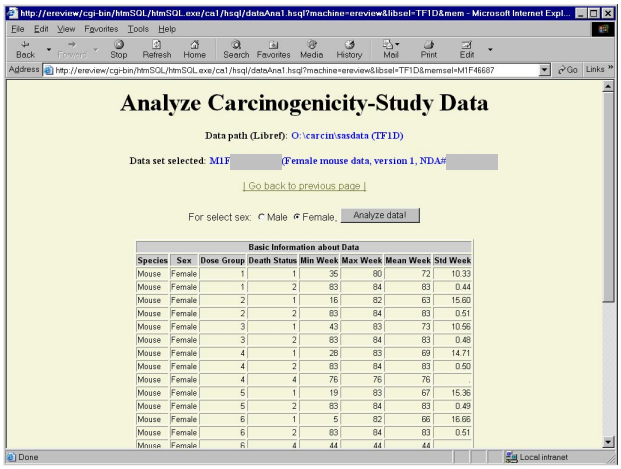
Working with the reviewing pharmacologist, the decision of combining organ or tumor types can be easily made online.



When the decisions are made and a new data set is saved, the reviewers can view the counts of tumor-bearing animals for combined organ or tumor types. The combined organs or tumors are marked with a leading [C].



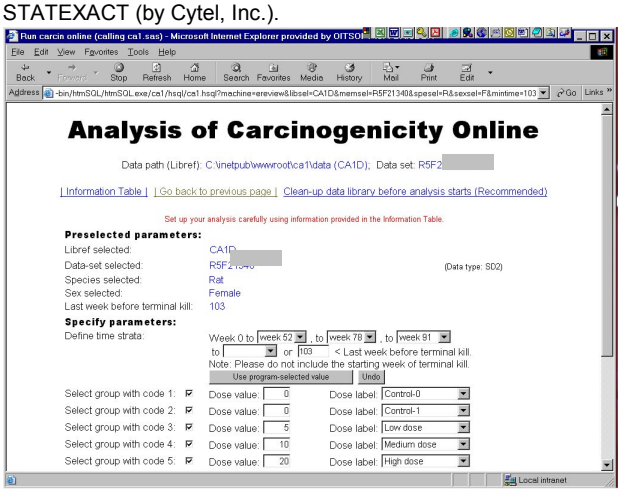
ANALYZE TUMOR DATA



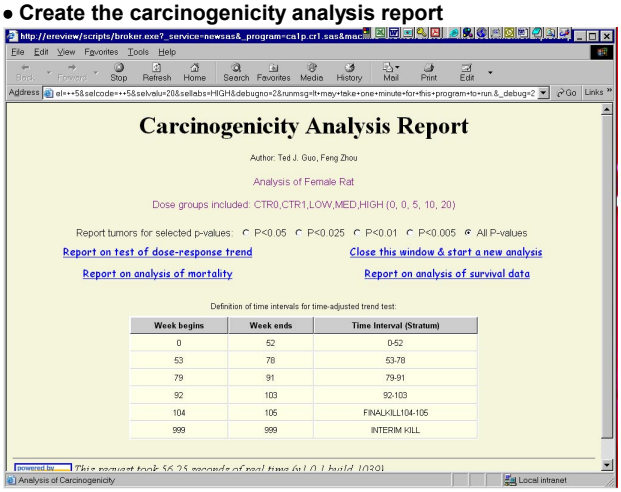
The analysis the carcinogenic potential of the testing drug in rats or mice for selected sex usually is based on analysis data with selected organs and tumors combined. WebCarcin provides the user with flexible options. The user can

- Reanalyze tumor data using the sponsor's setup, or
- Reanalyze tumor data using a different setup
- Create the carcinogenicity analysis report in Word® by copying and pasting the results from WebCarcin.

• **Reanalyze tumor data with flexible setup** – the user can select or enter parameters before submitting a run. SAS/IntrNet Application Dispatcher calls SAS programs including PROC STATEXACT (by Cytel, Inc.).



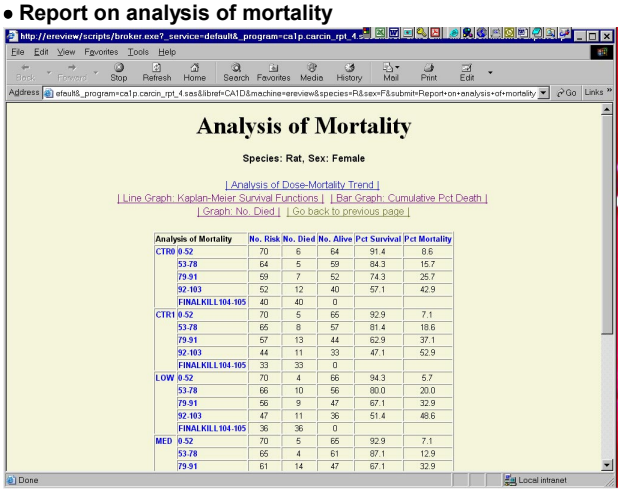
• **Create the carcinogenicity analysis report**

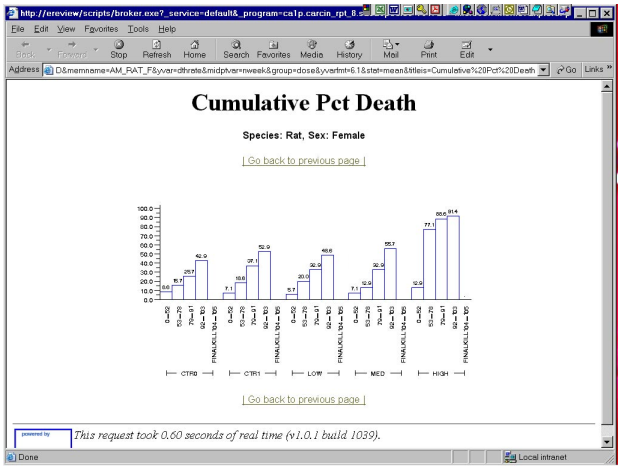


The carcinogenicity analysis report includes:

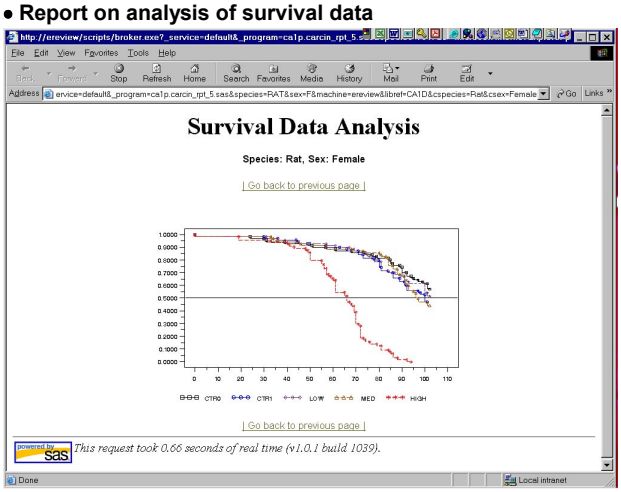
- Report on analysis of mortality
- Report on analysis of survival data
- Report on test of dose-response trend

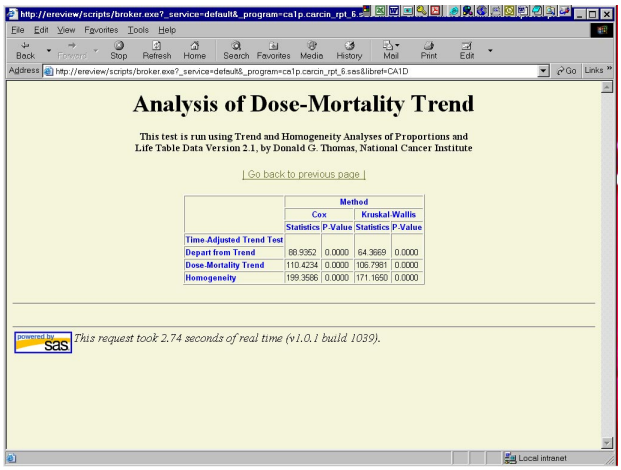
• **Report on analysis of mortality**



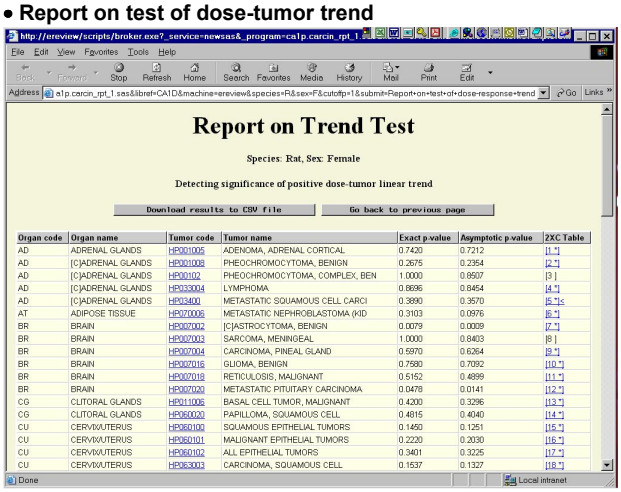


• **Report on analysis of survival data**





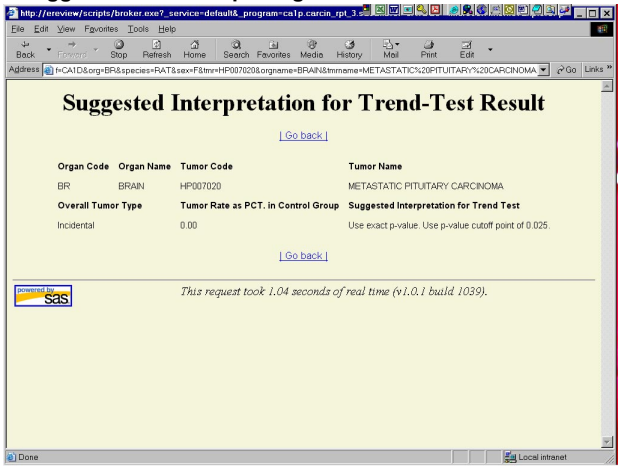
• **Report on test of dose-tumor trend**



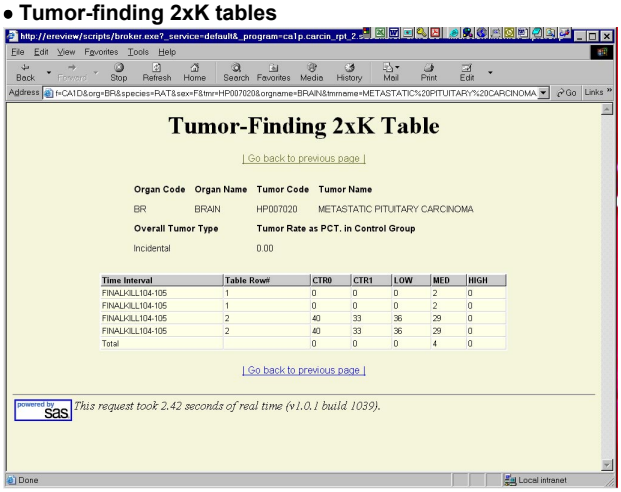
The user can also ask for information about

- Suggestions on interpreting the trend-test result
- Tumor-finding 2xK tables

• **Suggestions on interpreting the trend-test result**



• **Tumor-finding 2xK tables**



CONCLUSION

WebCarcin, developed using Application Dispatcher and htmSQL, delivers both data and application services to FDA's statistical and non-statistical reviewers for regulatory reviews in an efficient and effective way. Not only does it allow for interactions between the individual user and the SAS system, but also it enables interactions among users. SAS/IntrNet provides an ideal computational environment for regulatory agency like FDA.

ACKNOWLEDGMENTS

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ADDITIONAL INFORMATION ABOUT WEB-BASED PROGRAMS AT CDER/FDA

http://eReview/Stability -for online analysis of drug stability
http://eReview/Nda - for online analysis of clinical data (under development)
http://eReview/SafetyAE - New ongoing project

[1] The data set used in this paper is fictitious and not from any real NDA/IND submission.