

Prior to initiating the testing of a substance, an NIEHS/NTP staff scientist develops a research concept document. This research concept outlines the general elements for a program of study of the substance to address specific research needs raised in its nomination to the testing program. Additional information about the nomination, review, and selection of substances for study by the NTP is provided from *Nominations to the NTP Testing Program* (<http://ntp.niehs.nih.gov/go/nom>).

NTP Concept Document: Gum Guggul

Gum guggul is a dietary supplement with expanding use in the U.S., primarily for treatment of hyperlipidemia, but it has also been used to treat arthritis, obesity, coronary artery disease, and nodulocystic acne. Gum guggul was nominated to the National Toxicology Program for toxicological characterization based on expanding use and lack of available information to adequately assess safety in humans. Gum guggul is primarily available commercially as a crude resin from the *Cammiphora mukul* tree or an ethyl acetate extract of the resin. Guggulsterones are the active compounds responsible for the hypolipidemic activity.

Gum guggul has a broad spectrum of molecular and biological activities. Mechanistic research suggests that the hypolipidemic activity of gum guggul involves modulation of cholesterol and bile acid homeostasis via an interaction with the farnesoid X receptor (FXR) and the pregnane X receptor (PXR). Modulation of PXR and the 3A family of cytochromes P450 suggest that there is a significant potential for drug-drug or drug-chemical interactions. Gum guggul and guggulsterones also interact with the androgen receptor, estrogen receptor-alpha (ER α), progesterone receptor, glucocorticoid receptor, mineralocorticoid receptor, and constitutive androstane receptor (CAR). Based on the interaction with sex hormone receptors, there are concerns regarding potential reproductive effects of gum guggul. Additional biological effects of gum guggul include effects on thyroid hormone homeostasis, platelet aggregation, carbohydrate metabolism, and inflammation. No information regarding genotoxicity, immunotoxicity, ADME, or chronic exposure is currently available.

The following areas of research were proposed by the project leader and discussed at the meeting. The group recommended a tiered research approach in prioritizing the study needs for gum guggul. Tier I includes studies that were considered the highest priority, whereas the Tier II includes studies that might be reconsidered as data is available from the Tier I studies.

- 1) The inclusion of additional endpoints (ie. -thyroid hormone levels, blood clotting parameters, CYP expression, etc.) to standard toxicology studies to address the broad spectrum of reported effects in various organ systems. These studies were considered a high priority in the research program.
- 2) As a promiscuous ligand for various nuclear receptors, which regulate gene expression, gum guggul should be considered for toxicogenomic evaluation. These studies were considered unfocused at this time and should be revisited if reproductive or developmental toxicity is observed.
- 3) Mechanistic research with regard to interaction with nuclear receptors including the consideration of outside collaboration or a small grant program. The existing data for nuclear receptor interactions was considered adequate without further demonstration of toxicity.

Further research might be warranted depending on the results from *in vivo* toxicity studies.

4) Potential drug-drug or drug-chemical interactions due to the activation of PXR and induction of CYP 3A. The potential for drug and chemical interactions is of considerable interest. Further investigation of these effects was considered a high priority.

5) Investigate the activity profile for gum guggul on enzymes involved in sex hormone biosynthesis. These endpoints may be included in additional endpoints to the standard toxicology studies, or may be a part of the second tier.

6) Segment I, II, and III testing to determine effects on fertility and reproduction, teratogenicity, and perinatal development. Reproductive and developmental studies were considered a high priority, with developmental studies selected as the highest priority.

7) ADME, immunotoxicity, genotoxicity, and carcinogenicity studies due to the lack of information currently available. Immunotoxicity studies were considered a high priority which could be incorporated into developmental studies. The Salmonella assay, as part of the standard toxicology testing strategy, was suggested. No special genotoxicity studies were recommended. It was suggested that ADME be considered if further studies on the biologically active components of the gum guggul extract are planned. Carcinogenicity studies were considered a low priority, but a 2-year study was suggested to evaluate chronic toxicity.

8) Consideration of diet selection and the utility of alternative models such as a hyperlipidemic and/or obesity model on gum guggul toxicity. It was recommended that these studies be considered if initial toxicology studies are positive.

Study recommendations:

Tier I:

- 1) Developmental toxicology (highest priority) including developmental immunotoxicity
- 2) Subchronic toxicology studies with consideration of a longer duration (6-months or 2-years). These studies should include additional endpoints to address the broad biological activities of gum guggul and standard genotoxicity testing.
- 3) Evaluation in drug interaction panel.

Tier II:

- 1) Mechanistic studies on the interaction of gum guggul with nuclear receptors
- 2) Identification of the active compounds of the extract responsible for the biological/toxicological activities (which could include the guggulsterones)
- 3) ADME studies
- 4) Consideration of alternative animal models

These studies will be conducted with the ethyl acetate extract of gum guggul, which is the primary commercially available form. For *in vitro* and mechanistic studies, the purified guggulsterones, which are available commercially, should be considered. The utility of toxicogenomics studies was discussed. These studies would be considered useful if developmental toxicity was observed. Carcinogenicity studies were considered a low priority.

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