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## **New Substances Nominated to the NTP for Toxicological Studies**

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**Dr. Scott Masten**

**NTP Board of Scientific  
Counselors Meeting**

**August 18, 2005**



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## **Nominations for NTP Toxicology Studies**

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- ◆ **Formal open process for soliciting, receiving and reviewing nominations for new toxicology studies**
  - **NIEHS and Interagency committee reviews**
  - **NTP Board of Scientific Counselors review**
  - **Public comment period**

## New Study Nominations

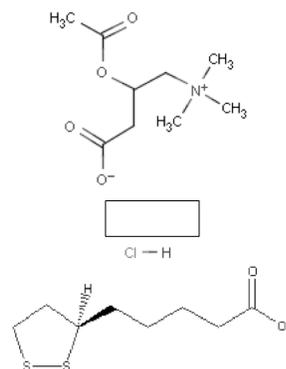
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- ◆ 15 new nominations
  
- ◆ Primary use/exposure scenario
  - Dietary supplements (5)
  - Consumer products (4)
  - Industrial chemicals (6)
  
- ◆ Review by the ICCEC March 2005
  - Recommended for study (11)
  - Deferred until further information available (3)
  - No studies at this time (1)

## Acetyl-L-Carnitine and $\alpha$ -Lipoic Acid

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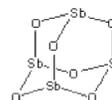
- ◆ Nominated by: NCI
  
- ◆ Rationale: Increasing dietary supplement use, esp. older individuals
  
- ◆ Study Recommendations: Subchronic toxicity, individually and in combination, with focus on thyroid effects



## Antimony Trioxide

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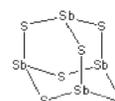
- ◆ **Nominated by: NIEHS**
- ◆ **Rationale: Significant occupational exposure; no 2-year carcinogenicity studies**
- ◆ **Study Recommendations: Chronic toxicity, carcinogenicity, cardiotoxicity**



## Antimony Trisulfide

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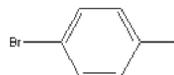
- ◆ **Nominated by: NCI**
- ◆ **Rationale: Significant occupational exposure; suggestive but insufficient evidence of carcinogenicity**
- ◆ **Study Recommendations: No studies; study of antimony compound with higher exposure potential more appropriate**



## 4-Bromofluorobenzene

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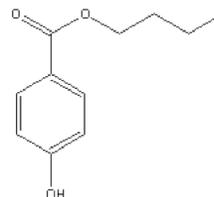
- ◆ **Nominated by: NIEHS**
- ◆ **Rationale: High production volume; suspicion of toxicity/carcinogenicity based on structure**
- ◆ **Study Recommendations: Defer; additional information anticipated through HPV chemical initiatives**



## Butylparaben

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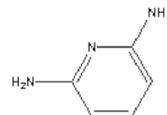
- ◆ **Nominated by: NIEHS**
- ◆ **Rationale: Widespread exposure via personal care products, OTC drugs, foods; further data needed on potential reproductive effects**
- ◆ **Study Recommendations: Toxicological characterization including reproductive toxicity**



## 2,6-Diaminopyridine

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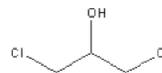
- ◆ **Nominated by: NCI**
- ◆ **Rationale: Moderate production/use; mutagenic; limited data**
- ◆ **Study Recommendations: Defer; seek additional information on exposure from use of hair dyes**



## 1,3-Dichloropropanol

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- ◆ **Nominated by: NIEHS**
- ◆ **Rationale: High production/use; contaminant in foods; suggestive evidence for carcinogenicity, reproductive toxicity**
- ◆ **Study Recommendations: Toxicological characterization including reproductive toxicity, metabolism/disposition, carcinogenicity**

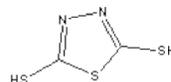




## 2,5-Dimercapto-1,3,4-thiadiazole

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- ◆ **Nominated by: Commercial Firm**
- ◆ **Rationale: Moderate production and use in wildland fire-fighting, other industries; limited data**
- ◆ **Study Recommendations: Genotoxicity; metabolism/disposition; subchronic toxicity**



## 3-Dimethylaminopropylamine

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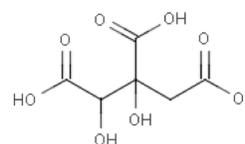
- ◆ **Nominated by: NCI**
- ◆ **Rationale: Use in personal care and industrial products; limited data; toxicity observed in exposed workers**
- ◆ **Study Recommendations: Genotoxicity; dermal absorption/metabolism; evaluate nitrosamine formation**



## ***Garcinia cambogia* extract**

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- ◆ **Nominated by: NCI**
- ◆ **Rationale: Increasing dietary supplement use; limited toxicity data**
- ◆ **Study Recommendations: Defer; review recent hydroxycitrate studies**



**(-)-Hydroxycitric acid**

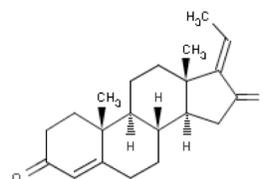
## **Gum Guggul Extract**

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- ◆ **Nominated by: NIEHS**
- ◆ **Rationale: Increasing dietary supplement use; metabolic and hormonal activity; limited toxicity data**
- ◆ **Study Recommendations: Toxicological characterization**



***Commiphora mukul***

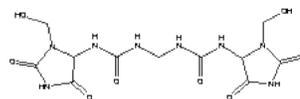


**Guggulsterone**

## Imidazolidinyl Urea

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- ◆ Nominated by: NCI
- ◆ Rationale: Widely used in personal care products; mutagenic potential
- ◆ Study Recommendations: Genotoxicity; dermal absorption; evaluate degradation products in test systems



## Permanent Makeup Inks

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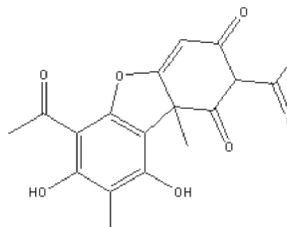
- ◆ Nominated by: FDA
- ◆ Rationale: Rapidly growing practice; adverse events reports; lack of safety data
- ◆ Study Recommendations: Product chemistry; *in vitro*/*in vivo* allergenicity, photoallergenicity, phototoxicity



## Usnic Acid and Usnea herb

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- ◆ Nominated by: FDA
- ◆ Rationale: Wide use in dietary supplements, personal care products; adverse events reports; lack of safety data
- ◆ Study Recommendations: Toxicological characterization including genotoxicity, pharmacokinetic, developmental and reproductive toxicity; *in vitro* toxicity (mitochondria)



Usnic acid

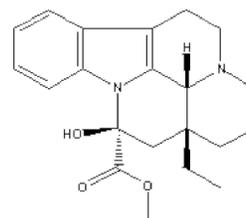


Usnea barbata

## Vincamine

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- ◆ Nominated by: NCI
- ◆ Rationale: Dietary supplement promoted as nootropic; limited long-term safety data
- ◆ Study Recommendations: Integrate with current QT interval prolongation research program





## Public Comments

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- ◆ **International Antimony Oxide Association**
  - Supports recommended studies
  - Review/comment on existing database
  
- ◆ **Cosmetic, Toiletry and Fragrance Association**
  - Butylparaben, Imidazolidinyl urea
    - Unpublished study reports
  
- ◆ **InterHealth Nutraceuticals**
  - *Garcinia cambogia* extract
    - Published articles



## Questions and Comments

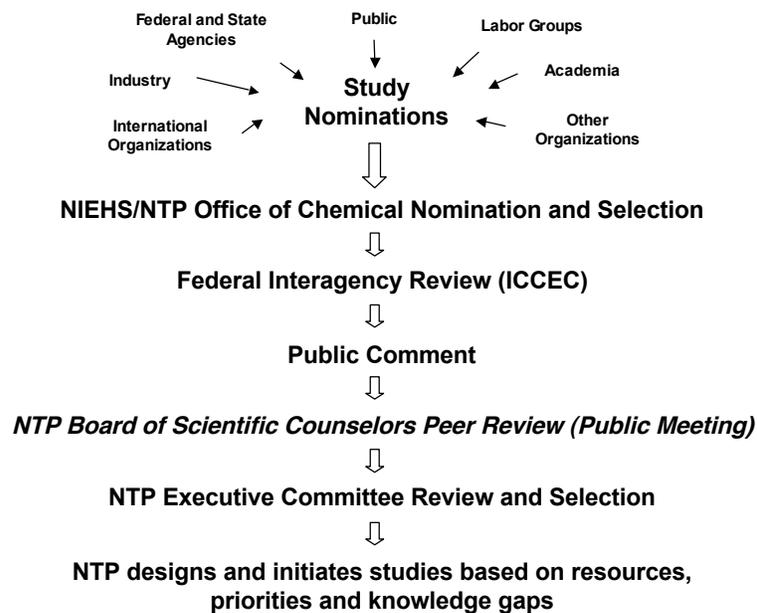
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## Questions for the Board

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- ◆ Does the Board agree with the recommended studies?
- ◆ Are there other studies that should be conducted on any of these substances?
- ◆ Are there some studies that should have higher priority than others? Which ones and why?

## NTP Study Nomination and Selection Process





## NTP Study Nomination Principles

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- The NTP operates under the principle that industry will evaluate chemicals or other agents for health and environmental effects as intended and mandated by Congress under legislative authorities. Therefore the NTP solicits and considers nominations for NTP studies from the following categories:
  - > Chemicals found in the environment that are not closely associated with a single commercial organization
  - > Biological or physical agents that may not be adequately evaluated without Federal involvement
  - > Commercial chemicals with significant exposure that were first marketed prior to current testing requirements or those which generate too little revenue to support further evaluations
  - > Potential substitutes for existing chemicals or drugs that might not be developed without Federal involvement
  - > Substances that occur as mixtures for which evaluations can not be required of industry
  - > Chemicals or agents that will aid our understanding of chemical toxicities, or our understanding of the use of test systems to evaluate potential toxicities
  - > Chemicals that should be evaluated to improve the scientific understanding of structure-activity relationships, and thereby help limit the number of chemicals requiring extensive evaluations
  - > Emergencies or other events that warrant immediate government evaluation of a chemical or agent
- The NTP will assess the specific needs for studies, evaluate existing literature and testing data, assess ongoing evaluations in the government and private sector, and also determine how the chemical fits into an overall plan for improving the test systems before committing to specific studies. The selection of a chemical or agent by the NTP Executive Committee does not automatically commit the NTP to evaluate that chemical or agent. The priority of the chemicals and the proposed studies are assessed during the nomination process and reassessed during the study design process and during the selection of contractors to conduct the studies. During any of these phases the chemical or study may be withdrawn if higher priority studies are found, or if the study proves to be impractical.