

# Resorcinol Task Force

*Society of Toxicology Meeting, Pittsburgh Chapter*

*Friday 18<sup>th</sup> October 2002*

## ***'Resorcinol: - a case study in managing toxicological issues in the regulatory environment'***

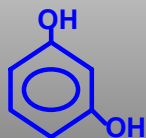
*by*

*Paul Ashford – Manager, Resorcinol Task Force*

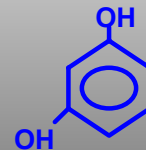


# Objectives of this presentation

- ◆ To use the resorcinol case study to illustrate that the growth of regulatory concern does not necessarily require new findings
- ◆ To emphasize how difficult it can be to satisfy these concerns
- ◆ To highlight the growing need for high quality toxicological data in the global regulatory arena
- ◆ To give some insights into the likely future direction of European Chemical Policy and the implications for the toxicology community



**RESORCINOL TASK FORCE**



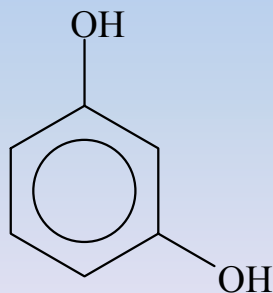
# What this presentation is not!

- ◆ It is not a detailed consideration of the toxicological aspects of resorcinol
- ◆ It is not an attempt to predict the regulatory outcome of the treatment of resorcinol either in Europe or elsewhere
- ◆ It is not an exhaustive review of the European regulatory scene, since this has at least 15 separate components ...called Member States!

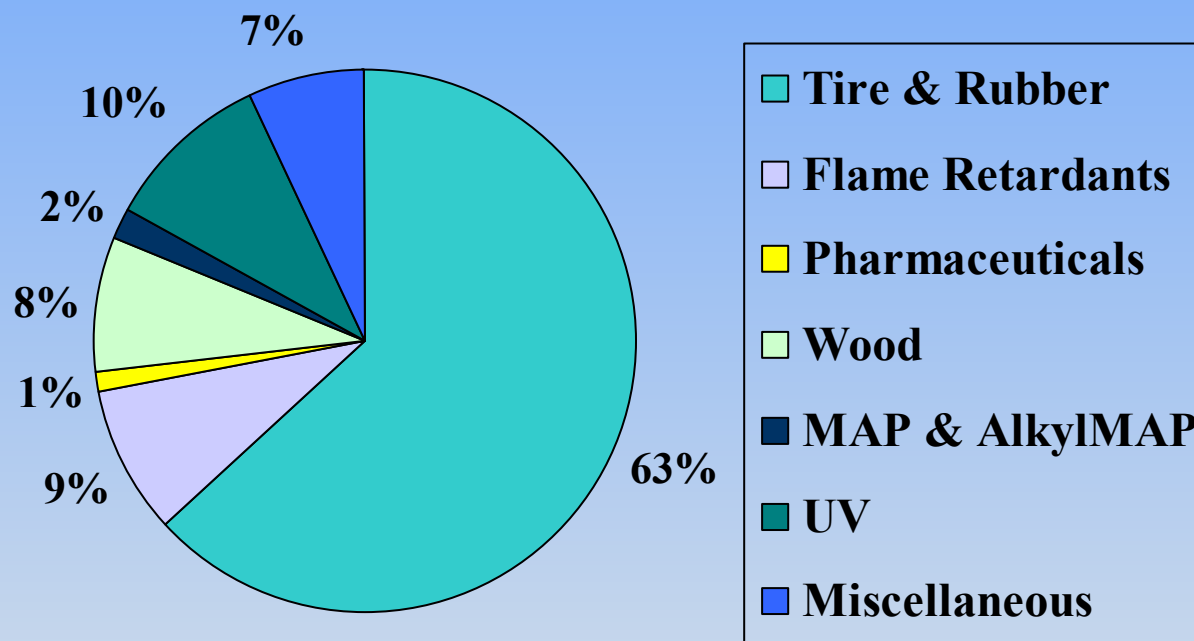


# Resorcinol - What is it?

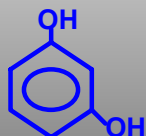
- ◆ Otherwise known as 1,3 - dihydroxybenzene
- ◆ EINECS No. 203-585-2; CAS No. 108-46-3
- ◆ White crystalline solid with melting point  $\sim 110^{\circ}\text{C}$
- ◆ Manufactured in the US and Japan by three major producers
- ◆ Occurs naturally in coal shale and is reportedly present as a by-product in cigarette and wood smoke



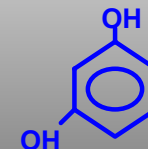
# Resorcinol - Where is it used?



Approximately 13,000 tonnes imported into the EC  
(no European producer)

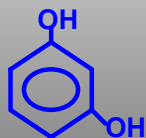
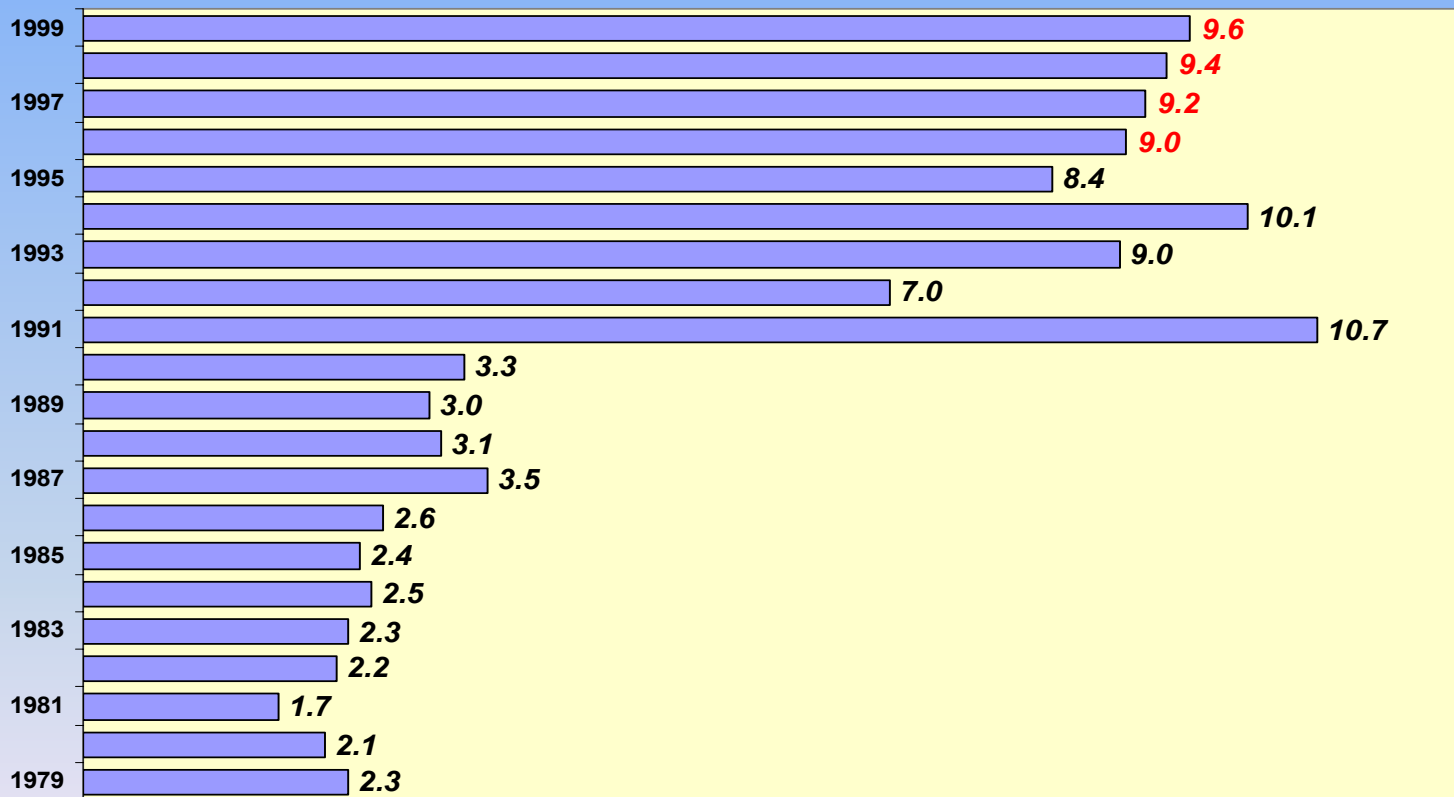


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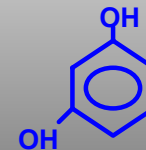


# Resorcinol - Supply History

Resorcinol Imports into Western Europe  
(thousands of metric tons)

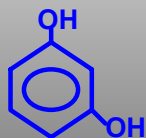


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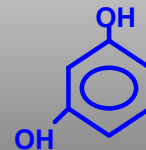


# Resorcinol - General Observations

- ◆ Usage dates back well into the 19<sup>th</sup> century in pharmaceutical and other uses
- ◆ Classical 'industrial chemical' of low toxicological concern
- ◆ Covered by several relevant Council Directives:
  - *Council Directive 76/768 - Cosmetic uses*
  - *Commission Directive 90/128/EEC - Food contact (SML 2.4mg/kg - Section A)*
  - *Commission Directive 91/332/EEC - Occupational Exposure (Limit Value 10ppm 45mg/m<sup>3</sup> based on 8 hr reference)*
  - *Council Directive 67/548/EEC and Council Regulation EEC/793/93 - Labelling*

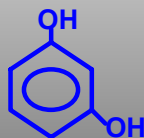


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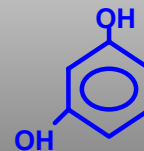


# Resorcinol - Toxicology

- ◆ Strong skin and eye irritant
- ◆ Moderate acute toxicity (oral)
- ◆ Not understood to show estrogenic or anti-estrogenic activity
- ◆ Non-carcinogenic
- ◆ Non-mutagenic
- ◆ Non-teratogenic (if this is correct terminology!)



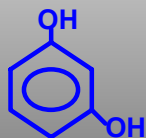
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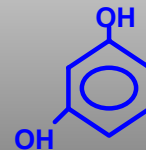


# Resorcinol – So why all the concern?

- ◆ It has long been known that resorcinol can engender REVERSIBLE dose-related thyroid affects at high and persistent exposures.
- ◆ Medical case studies available from the late nineteenth century.
- ◆ Only areas where skin exposures meet these criteria are in topical ointments for the treatment of acute skin lesions.....



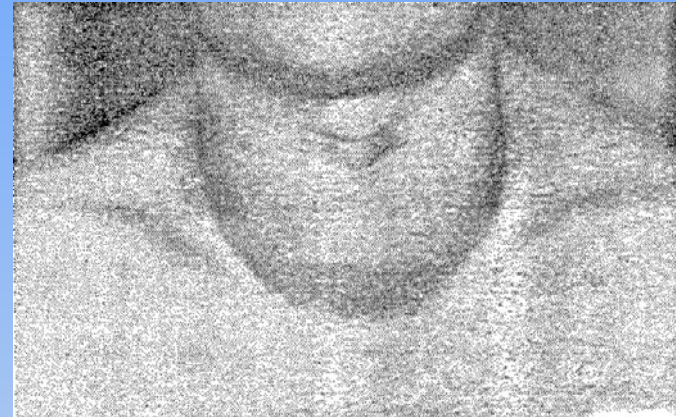
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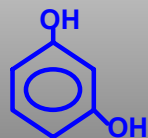
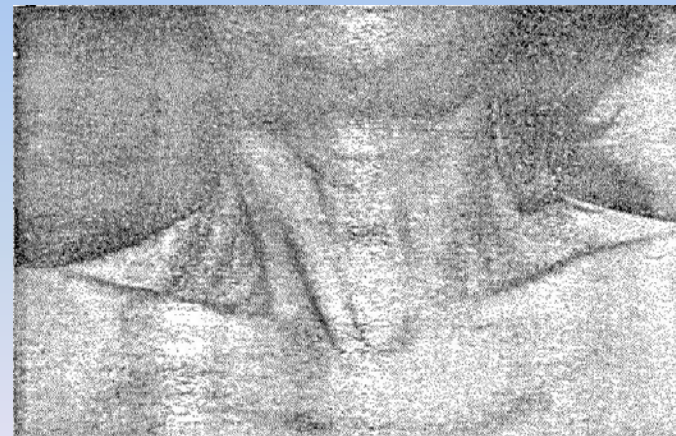
# Resorcinol - Reversible Hypothyroidism



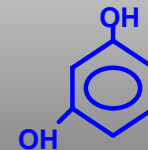
Fig. 1—Extensive ulceration of both legs.



2—Diffuse thyroid enlargement while the patient was still using resorcinol ointment.

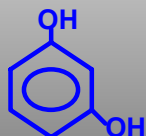


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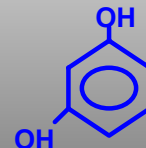


# Resorcinol – So why all the concern?

- ◆ It has long been known that resorcinol can engender REVERSIBLE dose-related thyroid affects at high and persistent exposures.
- ◆ Medical case studies available from the late nineteenth century.
- ◆ Only areas where skin exposures meet these criteria are in topical ointments for the treatment of acute skin lesions.
- ◆ All of this has been known for 50+ years and has already been considered in forming current regulations.
- ◆ So what's new? .....

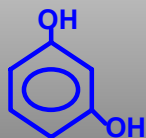


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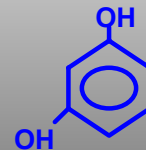


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# Resorcinol – So why all the fuss?

- ◆ After a long debate in the relevant Scientific Committee advising the European Commission (the CSTEE) it was decided to include the thyroid within the regulatory definition of the endocrine system.
- ◆ Resorcinol was therefore identified as an endocrine disrupter.
- ◆ More importantly, it was identified as an endocrine disrupter which is not currently restricted or under risk assessment within the EU.
- ◆ Why should it have been ? Historically, it was treated as a chemical of low regulatory concern.
- ◆ But please observe – nothing had changed except the perspective



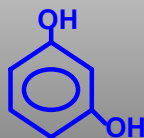
# Resorcinol Task Force (RTF)

- ◆ Formed to fulfill several parallel objectives:
  - *To provide information on the uses of resorcinol and any likely health and environmental issues arising*
  - *To seek to fill any potential data gaps in the toxicological and epidemiological data sets (also for HPV and ICCA)*
  - *To assist regulators in assessing the overall risks to human health and the environment posed by resorcinol*

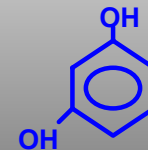


# RTF - Membership

- ◆ The three major global producers
  - *INDSPEC (United States)*
  - *Sumitomo (Japan)*
  - *Mitsui (Japan)*
- ◆ One significant user
  - *European Phenolic Resins Association (a CEFIC Sector Group)*
- ◆ Liaison with:
  - *Tyre industries in the United States (RMA) and now also in Europe (BLIC)*
  - *Hair Dye industry - global (HCTS)*
  - *Pharmaceutical industry in Europe (EFPIA)*
  - *Wood adhesives industry via CASCO*



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# RTF - Structure & Operations

- ◆ EPRA initially took the lead on European liaison because of geography
- ◆ Chairman of EPRA Technical Committee, Paul Ashford : - an independent consultant who has worked in the resins industry in technical and commercial roles for 20 years. Now a professional 'issue manager'.
- ◆ RTF soon outgrew EPRA and is now independently based on a joint research co-operation agreement between the producers.
- ◆ User groups (e.g. HCTS & EPRA) contribute to specific projects within the Task Force remit





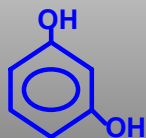
# RTF – General Positioning

- ◆ Has never publicly disputed the existence of a reversible dose-related thyroid effect.
- ◆ Has recognized that the CSTE decision regarding the inclusion of thyroid as part of the endocrine system is unlikely to change.
- ◆ Has recognized that there is a need to upgrade the basic toxicological dataset beyond a series of NTP Studies carried out by EPA in the early 1990s.
- ◆ Has decided to take a proactive role in filling the data gaps and work closely with all regulatory groups wherever possible.

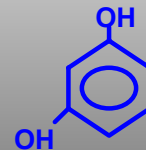


# RTF – Deliverables to date

- ◆ Carried out an initial and rapid in vitro screening study on wider endocrine effects (non GLP) (*August 1999*)
- ◆ Developed a Basic Resorcinol Status Report (*July 2000*).
- ◆ Commissioned a full, independent Literature Review with CANTOX (*August 2000*) – *shortly to be published in peer reviewed journal.*
- ◆ Carried out an initial environmental emissions review (*June 2002*)
- ◆ Carried out a review of data gaps and commissioned a compliant two generation drinking water study with WIL Research (*July 2002 – March 2004*)



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# RTF – Reprotox Study Outline

- ◆ 14-day Palatability Study already completed
- ◆ Dose Range Finding (DRF) Study to commence mid-October. To include significant neurotox end-points
- ◆ Protocol for compliant two-generation study to be finalized in Q2 2003
- ◆ In-life phase of compliant two generation study to complete by Q1 2004 with reporting to follow
- ◆ Frank Welsch (ex CIIT) acting as advisor and Study Monitor



# RTF – Communication with Regulators

- ◆ RTF recognized early-on the value of a formal Existing Substance Risk Assessment on resorcinol and sought to find Member State sponsors as early as August 2000.
- ◆ Some mild interest from Member States but no commitment at that time.
- ◆ Commission published a Communication on EDs in July 2001 that identified 9 industrial chemicals plus 3 hormones for specific review. The nine included resorcinol!
- ◆ WRc appointed in December 2001 to carry out a review in six months. Have liased closely based on CANTOX and other outputs



# RTF – Communication with Regulators

- ◆ WRc will publish its report around year-end and few surprises are expected. Have been able to get good 'buy-in' to the two-generation study protocol proposed by RTF.
- ◆ However, WRc are not allowed to make policy recommendations and a formal risk assessment is not a foregone conclusion.
- ◆ Some independent initiatives are already emerging at Member State level (e.g. a substance flow analysis has been just announced on resorcinol by the Danish EPA). These have been triggered by the July 2001 Commission Communication
- ◆ Occupational Health studies in both Germany and the Netherlands have basically confirmed low toxicological concern for workers.



# Resorcinol – Regulatory Implications

- ◆ RTF is hopeful that a formal risk assessment will put the (unchanged) risk back into context – particularly with more comprehensive GLP study outputs and environmental exposure data in place.
- ◆ However, if the risk assessment is not initiated before the introduction of the new European Chemicals Policy (2005) the hurdle may become higher
- ◆ The Commission has decided for the moment that EDs cannot be subject to authorisation under the proposed REACH system because there is no reliable legal definition
- ◆ There is possible interest at the European Chemical Bureau (ISPRA) for an ED classification and labeling initiative. However, this is being resisted on the basis that ED is not a toxicological end-point in itself.



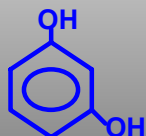
# Resorcinol – What have we learned?

- ◆ Well-established industrial chemicals of low toxicological concern are at risk if assessment criteria change
- ◆ There is a need to have better defined and more streamlined methods of upgrading toxicological data sets and initiating formal risk assessments.
- ◆ As risk assessments move progressively towards reaction intermediates and products, the burdens will only increase
- ◆ One estimate suggests that Research Laboratories could be full in Europe until 2030! Others suggest that the European Chemical industry will migrate to avoid the burden. However, controls are at market level so imported chemicals will be caught too (as resorcinol is now)

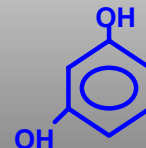


# Resorcinol – What have we learned?

- ◆ The on-going promotion of the Precautionary Principle means that chemical companies will only be able to extend their licenses to operate and never guarantee them into the future
- ◆ Member States are still free to go their own way (e.g. the Danish ‘undesirable chemicals’ list) and such actions are often more politically driven than science-based
- ◆ There needs to be a far better understanding of personal risk, risk assessment and risk management
- ◆ The chemical industry, more than ever before, needs to find new ways of communicating social relevance and value



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# A final thought...

Resorcinol may have been unfortunate to have been caught up in the new wave of regulatory fervor without any newly identified hazard, but it is only going along a path that many other chemicals will have to follow in the coming years.

Gone are the days when chemicals of low toxicological concern will be able to avoid the rigors of full hazard characterization. The most successful chemical companies will be those that embrace this new paradigm the quickest.

Resorcinol producers may yet look back on this episode with some satisfaction....



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Resorcinol producers may yet look back on this episode with some satisfaction....but try telling them that now!

