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Human health risk assessment of chloroxylenol in liquid hand soap and dishwashing soap used by consumers and health-care professionals

Lisa J. Yost [a, *], Joseph D. Rodricks [b], Duncan Turnbull [b], Paul C. DeLeo [c], J. Frank Nash [d], Antonio Quiñones-Rivera [e], Pete A. Carlson [f]

[a] Ramboll Environ, 333 W. Wacker Dr., Suite 2700, Chicago, IL 60606, USA
[b] Ramboll Environ, 4350 North Fairfax Drive Suite 300, Arlington, VA 22203, USA
[c] American Cleaning Institute, 1331 L Street, N.W., Sui te 650, Washington, D.C. 20005, USA
[d] The Proctor and Gamble Company, 11530 Reed Hartman Hwy., Cincinnati, OH 45241, USA
[e] GOJO Industries, One GOJO Plaza, Suite 500, Akron, Ohio, 44311, USA
[f] Ecolab, 370 Wabasha Street North, Saint Paul, MN 55102, USA

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ABSTRACT

A quantitative human risk assessment of chloroxylenol was conducted for liquid hand and dishwashing soap products used by consumers and health-care workers. The toxicological data for chloroxylenol indicate lack of genotoxicity, no evidence of carcinogenicity, and minimal systemic toxicity. No observed adverse effect levels (NOAEL) were established from chronic toxicity studies, specifically a carcinogenicity study that found no cancer excess (18 mg/kg-day) and studies of developmental and reproductive toxicity (100 mg/kg-day). Exposure to chloroxylenol for adults and children was estimated for two types of rinse-off cleaning products, one liquid hand soap, and two dishwashing products. The identified NOAELs were used together with exposure estimates to derive margin of exposure (MOE) estimates for chloroxylenol (i.e., estimates of exposure over NOAELs). These estimates were designed with conservative assumptions and likely overestimate exposure and risk (i.e., highest frequency, 100% dermal penetration). The resulting MOEs ranged from 178 to over 100, 000, 000 indicating negligibly small potential for harm related to consumer or health-care worker exposure to chloroxylenol in liquid soaps used in dish washing and hand washing.

1. Background

Chloroxylenol (4-chloro-3, 5-dimethylphenol or PCMX; CAS No. 88-04-0, see Fig. 1) is an antimicrobial chemical with a long history of safe use in topical antiseptic drug products for over-the-counter human use (FDA, 2013, 1994), and for pesticide use (EPA, 1994, 2009a, b). A human health risk assessment was conducted to evaluate the safety of chloroxylenol used as an active ingredient in rinse-off liquid antimicrobial hand soaps and dish soaps by consumer (adults and children) and in rinsed off antimicrobial liquid hand soaps by health-care workers. This assessment was initiated in response to the U.S. Food and Drug Administration (FDA) Proposed Rules and reopening of the administrative record on topical antimicrobial drug products for over-the-counter (OTC) human use (FDA, 2013, 2014) (hereafter Proposed Rules), which identified data needed to demonstrate that such antiseptics used in consumer and health-care settings are generally recognized as safe and effective [GRAS/E]. This paper focuses on the toxicity data available to evaluate the potential human health risks related to use of chloroxylenol in rinse-off liquid antimicrobial hand soaps and dish soaps. This work summarizes toxicological analyses conducted by scientific investigators worldwide and draws from those analyses to evaluate potential human health risks. This paper will provide analyses to support the assertion that although the toxicity data have limitations, taken together they are adequate to establish the safety of chloroxylenol in this use.

* Corresponding author.
E-mail addresses: lyost@ramboll.com (L.J. Yost), jrodricks@ramboll.com (J.D. Rodricks), dturnbull@ramboll.com (D. Turnbull), PDeLeo@CleaningInstitute.org (P.C. DeLeo), Nash.jf@pg.com (J.F. Nash), QuinonesA@gojo.com (A. Quiñones-Rivera), pete.carlson@ecolab.com (P.A. Carlson).

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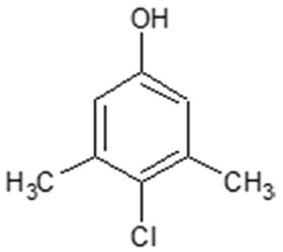

Fig. 1. Chloroxylenol.

2. Methods

This quantitative human health risk assessment includes (1) a hazard assessment to determine whether toxicity data for chloroxylenol are sufficient and derivation of no observed adverse effect levels (NOAELs), (2) an exposure assessment for consumer and health-care uses of liquid soaps containing chloroxylenol, and (3) calculation of the margin of exposure (MOE) for different product use scenarios, i.e., the ratio of the experimental NOAEL to the estimated human exposure level for each of the scenarios. An MOE approach is taken here it is typically used by the FDA, which has responsibility for regulating chloroxylenol in this use context.

3. Hazard assessment

A hazard assessment was conducted for chloroxylenol to evaluate all available toxicology data and consider the studies that could be used to establish a no observed adverse effect level (NOAEL) for chloroxylenol. Relevant reviews providing data on toxicity of chloroxylenol include the following: the Environmental Protection Agency (EPA) hazard and exposure evaluations for pesticide use (EPA, 1994, 2009a), the FDA (2013) analysis and request for data, a "white paper" risk assessment prepared by Exponent (2014), and a review by Guess and Bruch (1986).

3.1. Pharmacokinetic data on absorption, distribution, metabolism, and excretion (ADME)

Available data indicate that chloroxylenol is well absorbed orally and is rapidly metabolized. Specifically, oral studies conducted in rats and dogs show that chloroxylenol is rapidly metabolized, with as much as 100% of a 12 mg/kg oral dose of chloroxylenol in Dettol™[1] absorbed and excreted within 24 h in beagles (Bruch, 1996). Earlier, Havler et al. (1974) performed a series of studies investigating the pharmacokinetics and metabolism of chloroxylenol when administered to rats and dogs orally or dermally. In both species, orally administered chloroxylenol was rapidly and well absorbed, with peak plasma concentrations occurring at about 30 min after dosing in rats and 45–60 min in dogs, and was practically all excreted in the urine within 24 h.

When radiolabelled chloroxylenol in Dettol™ was applied to the backs of rats under an occlusive patch, peak plasma concentrations were reached 2 h after administration, about 50% of the applied dose was absorbed within 6 h, and as with oral administration, excretion in urine was complete within 24 h (Bruch, 1996). The half-life in plasma was calculated as 60 min in rats and 50 min in dogs. Analysis of urine samples collected from rats and dogs over the 24 h following dosing showed similar metabolic pathways, with excretion in urine as a 6:1 mixture of glucuronide and sulfate conjugates, together with very low levels of free chloroxylenol. A cross-species *in vitro* study in rat, mouse, and human liver microsomes by Thomas and Kotchevar (2010) indicated that the identity of metabolites and their concentrations in liver microsomes from all three species were similar.

The metabolism of chloroxylenol is rapid (FDA, 2013; EPA, 1994; Dorantes and Stavchansky, 1992; Bruch, 1996). This may complicate attempts to measure dermal absorption of low concentration materials. For this quantitative risk assessment, oral and dermal absorption are assumed to be equivalent. This approach has been applied in this assessment in order to not underestimate risks, and is instead likely an overestimate of exposure and risk from dermal exposure.

4. Toxicity studies of chloroxylenol

4.1. Acute toxicity studies

Available acute exposure studies, lethality or LD_{50} studies, indicate low acute toxicity of chloroxylenol and provide some useful information on organ systems affected at such lethal doses. A summary of the LD_{50} and lethality data was completed in 1986 by Guess and Bruch, and similar summaries appear in the Handbook of Disinfectants and Antiseptics (Bruch, 1996) and the EPA Reregistration Eligibility Decision (RED) for chloroxylenol (EPA, 1994) (Table 1).

As presented in Table 1, LD_{50} values were greater than 2 g/kg in oral or dermal studies. The oral gavage study with an LD_{50} 3.83 g/kg study summarized in Bruch (1996) provided some information about toxicity in study animals including depression, depressed righting, and other reflex depressions, suggesting central nervous system toxicity as the cause of death. Gross autopsies on all rats that died prior to study termination showed congested lungs, gastrointestinal irritation, dark livers, congested adrenals, and hemorrhagic kidneys. Gross autopsies conducted on animals surviving to termination of the 14-day experiments showed no significant pathologic changes.

4.2. Subchronic toxicity studies

Available subchronic toxicity studies have reported low systemic toxicity in animals after percutaneous, oral, or dermal exposures with observed changes only found at dose levels near the LD_{50}. EPA (2009a) reported an oral NOAEL of 1250 mg/kg-day for a 90-day toxicity study in rats administered chloroxylenol at 23, 1250 and 2500 mg/kg-day (MRID 00141330 in EPA, 2009a). EPA (2009a) reported a lowest observed adverse effect level (LOAEL) of 2500 mg/kg-day based on increased relative and absolute liver weights in high-dose males and increased relative kidney weights.

Morris (2001) reported a 13-week study was conducted with 10 Crl:CD®-1 (ICR)BR mice exposed dermally to concentrations of 0, 15%, 30%, and 60% chloroxylenol in 10 μL acetone (0, 250, 500, and 1000 mg/kg bw/day). Findings included dermal irritation described as "very slight erythema and edema" at the 250 and 500 mg/kg-day dose levels, while animals dosed at the 1000-mg/kg bw/day dose level showed thickening and scabbing of the skin. In a 21-day and 90-day subchronic dermal exposure study in rabbits, local erythema, coriaceous area, and fissuring were observed at 180 mg/kg-day (LOAEL), with a NOAEL identified at the next lowest dose level of 18 mg/kg-day (Doyle and Elsea, 1965; EPA, 2009a; MRID 40223124).

[1] Dettol TM: This is a commercial product that contains chloroxylenol and pine oil. Bruch (1996) notes that many studies were performed with a Dettol formulation containing 4.8% chloroxylenol, 10% alcohol, and 20% terpineol in a castor oil-based soap. They also note "The contribution of the other ingredients complicates the conclusions concerning chloroxylenol, but it should also be recognized that these additional ingredients would contribute to greater toxicity."