No. 20-16758

IN THE UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

NATIONAL ASSOCIATION OF WHEAT GROWERS, ET AL.,

Plaintiffs-Appellees,

v.

ROB BONTA*, ATTORNEY GENERAL OF CALIFORNIA, ET AL.,

Defendants-Appellants.

On Appeal from the United States District Court for the Eastern District of California, Case No. 2:17-cv-02401-WBS-EFB Honorable William B. Shubb

BRIEF OF CALIFORNIA LEAGUE OF FOOD PRODUCERS, CALIFORNIA MANUFACTURERS & TECHNOLOGY ASSOCIATION, CALIFORNIA RESTAURANT ASSOCIATION, CALIFORNIA RETAILERS ASSOCIATION, CIVIL JUSTICE ASSOCIATION OF CALIFORNIA, AMERICAN BEVERAGE ASSOCIATION, AMERICAN CHEMISTRY COUNCIL, AMERICAN FROZEN FOOD INSTITUTE, AMERICAN SPICE TRADE ASSOCIATION, CONSUMER BRANDS ASSOCIATION, CONSUMER HEALTHCARE PRODUCTS ASSOCIATION, COUNCIL FOR RESPONSIBLE NUTRITION, FROZEN POTATO PRODUCTS INSTITUTE, JUICE PRODUCTS ASSOCIATION, PEANUT AND TREE NUT PROCESSORS ASSOCIATION, AND SNAC INTERNATIONAL, AS *AMICI CURIAE* IN SUPPORT OF PLAINTIFFS-APPELLEES AND AFFIRMANCE

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*Following Defendant Xavier Becerra's confirmation as HHS Secretary, Rob Bonta was confirmed as the Attorney General of California on April 22, 2021. See Fed. R. App. P. 43(c).

CORPORATE DISCLOSURE STATEMENT

Pursuant to Rules 26.1 and 29(a)(4)(A) of the Federal Rules of Appellate Procedure, *amici curiae* state that none of them has a parent corporation and no publicly held corporation owns 10% or more stock in any *amici*.

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INTEREST OF AMICI CURIAE

Amici curiae submit this brief in support of Appellees and the decision of the district court.[1] *Amici* are sixteen California and national associations, including makers and sellers of foods, beverages, personal care and household products, consumer and commercial products, material and ingredients used therein, as well as operators of stores and restaurants. Together, companies represented by these associations play a vital role in the California and United States economies, contributing trillions of dollars in revenue and supporting tens of millions of jobs.

Amici are committed to supporting accurate communication about products sold, as well as product safety, consumer confidence and good jobs. *Amici* have been actively involved in Proposition 65 implementation for many years, ranging from at least ten years to the full thirty-four years Proposition 65 has existed. *Amici* and their members have been gravely impacted by Proposition 65's enormous economic and state-mandated speech burdens. Member companies' burden in trying to reach a resolution with Proposition 65 plaintiffs is further complicated because it simply is not possible for most member companies to print labels that are unique to the California market; while California residents may be accustomed to seeing these warnings, consumers in other states are not. Member companies have also been placed in the uncomfortable middle of disagreements

[1] No counsel of any party authored any part of this brief. No party or party's counsel, or person other than *amici*, contributed money that was intended to fund

between Proposition 65 plaintiffs or regulators, on the one hand, and national or other health authorities and expert agencies on the other hand. *Amici* and their members have seen how the improper, overly expansive implementation of Proposition 65 inflicts profound adverse consequences on companies doing business in California and on California's economy and its consumers.

Retail

California Retailers Association is the only statewide association representing all segments of the retail industry, including general merchandise, department stores, mass merchandisers, online markets, restaurants, convenience stores, supermarkets and grocery stores, chain drug and specialty retail stores. It represents a quarter of California's employment and $330 billion worth of annual GDP.

Food and Beverage

California League of Food Producers advocates for California's food producing industry, representing the interests of large and small food processors and beverage producers. The California food industry has a $25.2 billion impact in direct value-added to California's economy, with $56.7 billion in additional value-added through indirect and induced impacts.

American Beverage Association represents America's non-alcoholic beverage industry: hundreds of beverage producers, distributors, franchise

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preparing or submitting this brief.

companies and support industries. There were 27,922 jobs provided by California's beverage industry in 2019, and $20.5 billion in direct economic impact.

American Frozen Food Institute, along with its affiliated organization the Frozen Potato Products Institute, represents America's frozen food and beverage makers: farmers, fruit and vegetable growers, makers of prepared meals, suppliers and distributors that provide over 670,000 American jobs.

American Spice Trade Association represents the interests of the U.S. spice industry and has approximately 200 members including companies that grow, dehydrate, and process spices.

Juice Products Association's international membership consists of major processors and distributors of a wide variety of fruit and vegetable juices, juice beverages, drinks and other fruit products.

Peanut and Tree Nut Processors Association represents owners, operators, and food safety professionals in the peanut, tree nut, and seed industry, and those who supply related equipment and services. Member's companies employ millions of people and generate billions of dollars worldwide.

SNAC International is the international trade association of the snack food industry, representing over 400 snack manufacturers, marketers, and suppliers worldwide.

Restaurants

California Restaurants Association helps restaurateurs navigate the sometimes treacherous waters of the hospitality industry; it is the most inclusive and powerful voice of restaurant operators in California.

Additional Critical Industries

California Manufacturers & Technology Association works with state government to develop balanced laws, and effective regulations to stimulate economic growth while safeguarding the State's environmental resources; it represents 400 businesses from the manufacturing community – a sector that generates more than $300 billion yearly employing more than 1.2 million Californians.

Civil Justice Association of California represents businesses, professional associations and financial institutions committed to making civil liability laws more fair, efficient and clear.

American Chemistry Council represents more than 170 companies engaged in the business of chemistry, which directly touches more than 96% of all manufactured goods. The American business of chemistry supports over 25% of the U.S. GDP and provides 544,000 skilled, good-paying American jobs.

Consumer Brands Association represents nearly 2,000 iconic brands. From household and personal care to food and beverage products, the consumer

packaged goods industry contributes $2 trillion to U.S. GDP and supports more than 20 million American jobs.

Consumer Healthcare Products Association is the national trade association representing the leading manufacturers and marketers of over-the-counter medicines, dietary supplements, and consumer medical devices.

Council for Responsible Nutrition is the leading trade association representing dietary supplement and functional food manufacturers and ingredient suppliers: more than 180 manufacturers and supporting companies for a variety of dietary ingredients and supplements important to consumers' health.

* * *

Pursuant to Federal Rule of Appellate Procedure 29(a)(2), the parties have consented to the filing of this amicus brief.

INTRODUCTION

Amici support truthful and non-misleading cancer warnings for Californians. In this case, however, Proposition 65 implementation has strayed from its clear language and legislative (*i.e.*, ballot) history, which require "known to cause cancer" warnings only for genuinely known carcinogens. By doing so, California has left the realm of what is "known", the centerpiece of and boundary for Proposition 65, and required a warning that is false, misleading, and a violation of the First Amendment. The district court was right.

The wayward implementation of Proposition 65 before this Court is so pronounced that the "alternative" warning on which the Attorney General relies for this appeal does not even pass the legal standard for valid warnings the Attorney General himself laid out in his regulations.

Proposition 65 puts companies like the Wheat Growers' members and *amici*'s members, in an impossible situation – forced either to expend substantial resources defending inevitable enforcement actions, provide a "known to cause" warning that falsely denigrates their products, or provide an "alternative" warning that does not comply with relevant regulations, is still false and misleading, and likely would be challenged by a court. The burdens Proposition 65 imposes on businesses in these circumstances are particularly acute because Proposition 65 creates strong incentives for private enforcement actions and, directly contrary to the First Amendment, places the burden on the private business to prove the

compelled warning is false or misleading, rather than requiring the State to prove the warning it compels is true.

Judges have critiqued the law's burdens on defendants in unusually strong terms, one describing it as enabling "judicial extortion" and others noting the law makes it "virtually impossible for a private defendant to defend a warning action" on the science. The judges' starkly negative assessment of defending a Proposition 65 warning case on the science arises from the punishingly expensive task of establishing a difficult and technical affirmative defense. This large monetary burden of presenting the relevant science combines with the peril of potentially astronomical penalties and the risk of liability for substantial attorneys' fees after a battle of experts to push companies strongly toward providing a "known to cause" warning, even when they would rather be silent because the science does not support the warning. Thus, the Court is presented with an unambiguous example of heavy burdens forcing companies to carry California's false and misleading risk message in violation of the First Amendment.

ARGUMENT

I. The district court's decision conforms with Proposition 65's clear language emphasizing "known" carcinogens and with what California voters were told.

A. The statute and ballot pamphlet

To its core, Proposition 65 is a law regarding what is "known," not what might be. Appellant's impermissible attempt to expand Proposition 65 to the realm

of debate, asking this Court to force a warning about a scientific disagreement rather than what is "known," directly contradicts the language of the statute and ballot pamphlet. The statute says:

> "No person in the course of doing business shall knowingly discharge or release a chemical known to the state to cause cancer . . . in to water." Cal. Health & Safety § 25249.5
>
> "No person in the course of doing business shall knowingly and intentionally expose any individual to a chemical known to the state to cause cancer . . . without first giving clear and reasonable warning . . . ." *Id.* § 25249.6.
>
> "Chemicals known to the state to cause cancer: . . . Glyphosate." Cal. Code Regs. tit. 27, § 27001(b).

The Proposition 65 campaign statement in the official ballot pamphlet told voters they were adopting a non-controversial information statute about known carcinogens. The very first sentence of the ballot information statement, written by the California Attorney General ("AG"), states that Proposition 65 "Provides persons doing business shall [not] expose individuals to chemicals known to cause cancer . . . without first giving clear and reasonable warning …." 2-ER-119.[2]

The lead proponents of Proposition 65 told voters it would not focus on "suspect" chemicals, and instead told voters that only "known" carcinogens would be impacted. This point was emphasized four times in the one-page's worth of text

[2] Proposition 65, Cal. Health & Safety Code §§25249.5 - 25249.13, also addresses reproductive toxicants and water discharges. Those matters are not at issue here and thus not discussed.

in the official voters' ballot pamphlet describing the affirmative and rebuttal arguments favoring Proposition 65:

> "There are certain chemicals that are scientifically known—not merely suspected, but known—to cause cancer . . . . Proposition 65 would: . . . Warn us before we're exposed to any of these dangerous chemicals."
>
> "Proposition 65 singles out chemicals that are scientifically known to cause cancer . . . ."
>
> "Proposition 65's new civil offenses focus only on chemicals that are *known to the state* to cause cancer . . . . Chemicals that are only suspect are not included" (emphasis in original).
>
> "Proposition 65 simply says that businesses shouldn't put chemicals that are scientifically known to cause cancer, or birth defects …. into your drinking water. And that they must warn you before they expose you to such a chemical."

2-ER-121-22. *People ex rel. Lungren v. Superior Ct.*, 14 Cal. 4th 294, 306 (1996) ("Further evidence of the Act's purpose and intent can be gleaned from the ballot materials").

There was no discussion of "probable" carcinogens, only repeated references to "known" carcinogens and a disavowal of "only suspect" and "merely suspect" carcinogens. Neither the AG nor his *amici*, however, mention this aspect of Proposition 65's ballot argument. Indeed, the AG *repeatedly* omits the proper description of the "probable carcinogen" assessment by the International Agency for Research on Cancer ("IARC") by saying IARC concluded glyphosate was "a carcinogen." AG Br. 1, 2, 3, 45, 49, 53, 55, 68.

The law voters intended to enact was starkly different from the law the AG now seeks to enforce. Voters were informed that IARC's "known" carcinogens that were "already listed" by IARC in 1986 were to be part of Proposition 65 and that "merely suspect" chemicals were not to be part of Proposition 65. 2-ER-121.

B. Neither IARC nor California made a "known to cause" finding

The district court's conclusion about what the First Amendment requires aligns in this case with Proposition 65's limitation of only communicating about *known* carcinogens. Although the AG exalts IARC's conclusion that "sufficient evidence" was present in animals,[3] the IARC Monograph does not directly answer the question "sufficient evidence for what?" It is clear from IARC's overall conclusion, though, that it believed the evidence was sufficient only to conclude

[3] IARC has lowered its standard for sufficient evidence since 1986, which has put IARC at greater risk of flagging "merely suspect" chemicals or departing from scientific consensus on what is known. *Compare* Preamble, IARC Monograph Volume 41 (1986) (https://publications.iarc.fr/59) *with* Preamble, IARC Monograph Volume 112 (2017) (4-ER-746). Volume 41, which immediately preceded California's vote on Proposition 65, emphasizes malignant tumors: "Sufficient evidence of carcinogenicity is provided when there is an increased incidence of malignant tumors . . . ." Volume 41 at 18. In contrast, Volume 112 (covering glyphosate) permits sufficient evidence to be found based in substantial part on benign neoplasms: "Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms . . . ." 4-ER-765; 6-ER-1139 (identifying sufficient evidence based on five tumor types, three of which were benign (*i.e.* not cancerous) tumors (adenomas in pancreatic islet cells, liver cells and thyroid C-cells)). The accuracy of the IARC Working Group's conclusions is the subject of significant debate. *See* generally Gary M. Williams, *et al*. (2016) *A review of the carcinogenic potential of glyphosate by four independent expert panels and comparison of the IARC assessment*, Critical Reviews of Toxicology, 46:sup1, 3-20 https://doi.org/10.1080/10408444.2016.1214677

that the chemical is a "probable carcinogen" in humans, not a "known carcinogen" in humans. 6-ER-1141.

Further, California has simply *assumed* that each chemical for which IARC identifies sufficient evidence in animals is a "known" animal carcinogen. Cal. Code Regs. tit. 27, § 25904(b). California does not independently evaluate whether IARC's determination supports a "known to cause" conclusion. *Id.* § 25904(c); Office of Environmental Health Hazard Assessment's ("OEHHA") Update to Final Statement of Reasons ("FSR") for Cal. Code Regs. tit. 27, § 25904, at 19 (July 21, 2015) (Labor Code listings "are ministerial in nature and OEHHA does not analyze the underlying scientific basis for the identification.").[4] In cases where IARC does not review a substantial body of contrary evidence concerning carcinogenicity, or where there is a sincere scientific debate concerning IARC's conclusions, both true here, one cannot say that IARC's "sufficient evidence" finding represents a conclusion by IARC or by California that the chemical is a "known" animal carcinogen, as opposed to a "merely suspect" animal carcinogen.[5]

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[4] https://oehha.ca.gov/media/downloads/crnr/072115fsorlaborcode.pdf

[5] The level of certainty reached by IARC in determining whether there is "sufficient evidence" regarding carcinogenicity is not what California voters would consider to be "known" to cause cancer. *See* Preamble, IARC Monograph Volume 112 (2017) [4-ER-746-768]; *see also* Julie E. Goodman, *et al.*, *Recommendations for further revisions to improve the International Agency for Research on Cancer (IARC) Monograph program*, Regulatory Toxicology and Pharmacology, Volume 113, June 2020, 104639, https://doi.org/10.1016/j.yrtph.2020.104639. IARC provides no confidence level for its "sufficient evidence" assessment and

The absence of a "known to cause" cancer evaluation by either IARC or California renders a Proposition 65 "known to cause" warning misleading or false, contrary to voters' intent and a violation of the First Amendment. *See Zauderer v. Office of Disciplinary Counsel of the Supreme Court of Ohio*, 471 U.S. 626, 651 (1985).

C. The AG's positions do not respect the "known to cause" boundary of Proposition 65

The AG asserts neither the First Amendment nor Ninth Circuit precedent "requires a consensus of scientific judgment - which may take decades to develop - before the State may require a business to provide . . . vital information to those being exposed to glyphosate." AG Br. 3. This argument overlooks Proposition 65's focus on "known carcinogens" and exclusion of those chemicals that are "merely suspect." None of the cases cited by the AG for the proposition that consensus is not required were implementing a law designed to communicate certainty through a "known to cause" warning mandate. The State's potential authority for communicating accurate scientific information to the public, absent a consensus, under some other law is not at issue here.

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specifically states that other information should be weighed along with IARC's input. 4-ER-78 ("These evaluations represent only one part of the body of information on which public health decisions may be based. . . . Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations."). Here, the district court properly followed IARC's admonition that its work "represent[s] only one part" of the scientific community's assessment and considered other scientific opinions in evaluating the accuracy of Proposition 65's "known to cause" warning.

The AG also asserts that voters communicated they want to hear from IARC regardless of whether or not other agencies agree. AG Br. 7. To the contrary, voters expressed a desire to hear only about "known carcinogens," not merely suspect carcinogens. Furthermore, the voters recognized Proposition 65's requirements must conform to federal law, which of course includes the First Amendment. Cal. Health & Safety Code § 25249.10(a) (warning requirement "shall not apply to . . . an exposure for which federal law governs warning in a manner that preempts state authority."). Indeed, the opinion cited by the AG only holds that voters wanted IARC-reviewed known carcinogens placed on the Proposition 65 list. *Monsanto v. OEHHA*, 22 Cal. App. 5th 534, 553-54 (2018). That opinion distinguishes this listing act from the warning requirement. *Id*. at 555-558.

D. Mission creep

The constitutional conflict here need not have happened. This case is an example of the implementation of a law expanding over time beyond the sensible boundaries of that law, thereby creating a constitutional issue. As the parties explained, glyphosate was added to the Proposition 65 list of "known carcinogens" through the Labor Code listing mechanism. SER732. From 1987 through 2002, the first sixteen years of Proposition 65 implementation, California treated the Labor Code listing mechanism as a way to initially populate the Proposition 65 list,

but not as a recurring fountain of new listings. *California Chamber of Comm. v. Brown ("CalChamber")*, 196 Cal. App. 4th 233, 245 (2011).

In 2003, however, OEHHA reversed that sixteen-year history and began to add chemicals to the Proposition 65 list based on a reinterpretation of its duties. *Id*. at 245-246. OEHHA's reinterpretation was challenged by the California Chamber of Commerce in 2008. *Id.* at 247. The challenge was not focused on a particular chemical, but instead focused on OEHHA's general authority to use the Labor Code as a continuing source of new listings. *Id.* Importantly, the *CalChamber* court did not have any specific information before it – as this Court does – that a particular chemical was not even "known to cause" cancer in animals, nor was it presented with any First Amendment concerns. The court stated that "the language [of Proposition 65] is ambiguous" as to whether the Labor Code should be a source of ongoing listings. *Id*. at 251. On a fuller record, the *CalChamber* court may well have reached a different conclusion. *Iancu v. Brunetti*, 139 S. Ct. 2294, 2301 (2019) (doctrine of constitutional doubt provides that in the face of ambiguity, statute must be construed so as to avoid the conclusion that it is unconstitutional).

II. The warning pressed by the Attorney General on appeal is false and misleading.

The district court correctly concluded (i) that the AG's proposed "alternative" warning is not purely factual and uncontroversial, and (ii) the proposal does not comply with the implementing regulations.

The AG's proposed warning is false and misleading. California has not made a "determination" concerning whether glyphosate is a "known carcinogen", in the way those words would be understood by Californians. Instead, California applied the auto-pilot, "ministerial" Labor Code listing mechanism, with no "known to cause" scientific review. Cal. Code Regs. tit. 27, § 25904; FSR for section 25904, *supra*, at 19 (Labor Code listings are "ministerial" and "OEHHA does not analyze the underlying scientific basis for the identification."). And, there are many scientific bodies—not one—in disagreement with IARC's conclusion of sufficient evidence.

The record relied upon by the district court clearly establishes that glyphosate is not a "known" animal or human carcinogen. Even IARC has *not* said that glyphosate is "known" to it to be a carcinogen in animals or humans. As the AG recognizes, the Occupational Safety and Health Administration views IARC's list as one of "potential carcinogens," not "known" carcinogens. AG Br. 20-21. To the extent OEHHA and California courts have interpreted IARC's "sufficient evidence" assessment to indicate "known to cause cancer" (*see id*. 9-11), that merely highlights Proposition 65's First Amendment tensions;[6] it does not mean

[6] *Amici* do not dispute here that California courts have held "known" animal carcinogens should be *placed on the Proposition 65 list* when it is appropriate to presume the animal data are relevant to humans. *See AFL-CIO v. Deukmejian*, 212 Cal. App. 3d 425, 430 (1989). However, California courts have not considered the question of what constitutes "clear and reasonable" *warning* for chemicals only "known" to cause cancer in animals. The AG cannot justify communicating a

there is no problem. The statutory provisions and interpretations cited by the AG cannot change the actual facts of what is and is not known.

Even if glyphosate were a "known" animal carcinogen, the record is clear that it is not a "known" human carcinogen. Even the outlying IARC opinion does not go that far. 6-ER-1141 (glyphosate placed in IARC's "probably carcinogenic" category, not its "known" category). Thus, the only warning option California has established to comply with the law, providing a "known to cause" warning to humans, would unquestionably be misleading and violate the First Amendment.

Furthermore, as the district court found, the AG's proposed "alternative warning" does not even comply with his own regulation opining on what the warning requirement means. In 2003, the AG adopted regulations concerning the settlement of Proposition 65 actions. Cal. Code Regs. tit. 11, §§ 3200-3205. Section 3202 of these regulations "provides additional information concerning the Attorney General's interpretation of the statute and existing regulations governing clear and reasonable warnings . . . ." Section 3202(b) states:

> "Certain phrases or statements in warnings are not clear and reasonable, such as (1) use of the adverb 'may' to modify whether the chemical causes cancer . . . ; (2) additional words or phrases that contradict or obfuscate otherwise acceptable warning language."

"known to cause" warning to humans based only on animal data. That is misleading. The cases cited by the AG for the proposition that known animal carcinogens should be placed on the Proposition 65 list *do not* stand for the notion that a "known to cause" warning *to humans* is appropriate under Proposition 65.

The AG warning's reference to the United States Environmental Protection Agency ("USEPA") clearly presents "additional words" that "contradict" the "acceptable warning language" of the safe harbor warning or equivalent "known to cause cancer" words. Thus, in any other circumstance, the AG would argue and a California court likely would find that the USEPA sentence in the AG's proposed warning represents "additional words . . . that contradict or obfuscate otherwise acceptable warning language." Cal. Code Regs. tit. 11, § 3202(b)(2). A secondary, but possible, interpretation of the AG-proposed warning is that glyphosate "may" cause cancer, which also would violate the AG's express guidance. *Id*. § 3202(b)(1). Either way, the AG's proposal cannot be squared with his own regulations.

If Proposition 65's warning requirement were as open and flexible as the AG contends, the resulting uncertainty would itself put businesses in an untenable position, because case-by-case determinations would need to be made either by a judge or OEHHA. Such a process would be horribly expensive, burdensome and uncertain. The penalty and attorneys' fees aspects of Proposition 65 create strong incentives for different eyes to disagree, and "clear and reasonable" would always be in the eyes of the beholder. When First Amendment freedoms are at stake, clarity is crucial; private speakers cannot be forced to guess what speech will subject them to liability. Even if it comported with the statute, the undefined

standard now offered by the AG would be void for vagueness. *Riley v. Nat'l Fed'n of the Blind of N.C., Inc.*, 487 U.S. 781, 793-94 (1988).

III. Proposition 65's substantial burdens violate companies' speech rights.

Proposition 65 and its regulations are dominated by fact-specific, case-by-case issues that require an expensive legal, factual and expert-based analysis. These rules are regularly subject to conflicting interpretations as between plaintiffs and defendants. The plaintiff's remarkably easy burden of proof and the uncertainty surrounding the inherent fact-based nature of a business's affirmative defense discourages companies from defending their right not to speak. Likewise, the risk of significant attorneys' fees liability and the risk of significant penalty liability all work together to strongly pressure companies to not contest Proposition 65's speech requirements.

A. Judges and the Governor recognize Proposition 65 is abused

Private enforcers' abuse of Proposition 65 was first noted in a judicial opinion by Judge Miriam Vogel in her 2001 dissent in a case concerning mercury in dental amalgam. She noted that Proposition 65, as interpreted and applied by California courts, "encouraged a form of judicial extortion." *Consumer Cause v. SmileCare*, 91 Cal. App. 4th 454, 478 (2001). She then quoted the AG's description of the defendant's burden in a Proposition 65 case at length, including that: "*This is a highly technical, scientific inquiry, and is not the same as*

presenting anecdotal evidence that a product is 'safe' under some other standard." *Id*. at 481-482 (emphasis in original).

Five years later, three other California judges described the heavy burdens of Proposition 65 on defendants:

> [T]he burden shifting provisions make it virtually impossible for a private defendant to defend a warning action on the theory that the amount of carcinogenic exposure is so low as to pose "no significant risk" (*see* § 25249.10, subd. (c)) short of actual trial. There is no way a defendant is going to be able to carry its burden on demurrer based on allegations in the complaint, and a defendant will probably not be able to carry that burden on summary judgment either. [¶] Rather, in a case of a negligible, even microscopic "exposure" (say, to lead in nonfriable dried paint), it may take a full scale scientific study to establish the amount of the carcinogen is so low that there is no need for a warning under [] section 25249.10. Needless to say, these provisions make the instigation of Proposition 65 litigation easy -- and almost absurdly easy at the pleading stage and pretrial stages.

Consumer Defense Group v. Rental Housing Industry Members, 137 Cal. App. 4th 1185, 1214 (2006) (citations omitted).

Although the AG touts his ability to send letters to plaintiffs commenting on the merits of their case, he did not supply the district court with evidence that such letters work. Indeed, after more than ten years of experience with the "certificate of merit" provision in Proposition 65 that allows the AG to send unenforceable letters to plaintiffs concerning the merit of their case, then Governor Jerry Brown, a former AG himself, repeated the well-known fact that Proposition 65 is broken and being abused by plaintiffs. His Office stated: "Proposition 65 . . . has been abused by some unscrupulous lawyers driven by profit rather than public health." SER716. It also said his administration would work with the Legislature "to

revamp Proposition 65 by ending frivolous 'shake-down' lawsuits." *Id*. The Governor himself said "Proposition 65 . . . [is] being abused by unscrupulous lawyers." *Id*. Unfortunately, the recognized abuses of Proposition 65 were not addressed by the Legislature and remain an even more pressing issue today. The AG's web site catalogues each Proposition 65 notice of intent to sue from private enforcers.[7] In 2013, the year Governor Brown aired his concerns about Proposition 65 abuse by unscrupulous lawyers, there were approximately 1,095 notices catalogued. In 2020, there were more than three times that–approximately 3,574 notices.

Contrary to the AG's assertions, his authority to write letters communicating his view that a case lacks merit has not prevented private enforcers from pursuing these cases. For example, in 2012, the AG's office sent a letter to a Proposition 65 plaintiff's counsel expressing "concerns" regarding a Second Supplemental Notice of Violation issued on behalf of his client, and specifically requesting that the notice be withdrawn. *See* April 4, 2012 AG Letter.[8] The AG stated that the plaintiff's risk assessment and analysis was "significantly flawed," demonstrating there was no "valid basis" for the notice. Despite this scathing correspondence, the litigation proceeded with plaintiff actively litigating the case until it finally settled almost a year later. *See Anthony Held v. Kiss Nail Products, Inc. et al.,* Marin

[7] https://oag.ca.gov/prop65/60-day-notice-search

[8] https://oag.ca.gov/sites/all/files/agweb/pdfs/prop65/vorhees_ltr_fnl.pdf?

Superior Court Case No. CIV 1101576. *See also* 1-ER-14, fn. 10 (*Physicians Comm. for Responsible Med. v. McDonald's Corp.*, Los Angeles Superior Court, Case No. BC383722 (lawsuit against restaurants lasting 6 years based on allegations that cooked chicken exposed Californians to listed carcinogen "PhIP," despite an AG determination that the level of PhIP in cooked chicken fell far below the level that would require a Proposition 65 warning); *Sciortino v. PepsiCo, Inc.*, 108 F. Supp. 3d 780 (N.D. Cal. 2015) (denying motion to dismiss where parties disputed whether defendant's products exceeded safe harbor level); *CKE Rests., Inc. v. Moore*, 159 Cal. App. 4th 262 (2008) (affirming dismissal of suit seeking declaration that plaintiff could not initiate Proposition 65 litigation because safe harbor level was not exceeded)).

B. Proposition 65 enforcers' burden of proof does not satisfy constitutional compelled speech standards

A plaintiff's pleading and courtroom burden under Proposition 65 is merely to demonstrate (1) exposure in any amount to a listed chemical, (2) by a person in the course of doing business, (3) without having provided a "clear and reasonable" Proposition 65 warning. Cal. Health & Safety Code § 25249.6. This burden has been accurately described as "almost absurdly easy." *Rental Housing Industry Members*, 137 Cal. App. 4th at 1215.

Proposition 65 allows, and the State has experienced, a significant number of enforcement actions for small chemical exposures that neither the State nor the private enforcer has established are "known" to pose a risk to humans. For

example, any "touch" is an exposure. Cal. Code Regs. tit. 22, § 25102(i). This has led to allegations that Disneyland should warn visitors who come to the Magic Kingdom on average once a year or less of the presence of lead in its brass hand rails, and allegations that the brass button one pushes to activate the walk sign when crossing a street requires a warning.[9] Similarly, any detectable part per billion or part per trillion can be an inhalation or ingestion exposure that shifts the burden of proof to defendant. *Id.* §§ 25102(i), 25900. This low bar for plaintiff's case has no relevance to causation at all, let alone the higher "known to cause" warning mandate.

As currently implemented, the burden of proof plaintiffs who represent all Californians carry under Proposition 65 does not satisfy the State's duty to demonstrate that compelled speech is factual and uncontroversial. *Nat'l Inst. of Family & Life Advocates v. Becerra*, 138 S. Ct. 2361, 2371 (2018).

C. Proposition 65's expensive affirmative defense and high potential monetary penalties force companies to adopt false and misleading speech

Defendants that elect not to provide a safe harbor warning are likely to face litigation. To defend litigation and establish the affirmative defense that the chemical present in a defendant's product in fact poses no significant cancer risk,

[9] Mateel Environmental Justice Foundation 60-Day Notice to Walt Disney Parks & Resort (February 20, 2013), https://oag.ca.gov/system/files/prop65/notices/2013-00208.pdf; Mateel 60-Day Notice for "Brass cross-walk pushbuttons" (April 7, 2000), AG No. 2000-00042, https://oag.ca.gov/prop65/60-day-notice-search.

defendants must hire several experts in the fields of toxicology, risk assessment and exposure assessment who in turn must undertake significant and expensive work. *See, e.g., People ex rel. Brown v. Tri-Union Seafoods, LLC*, No. CGC-01-402975, 2006 WL 1544384 (Cal. Super. Ct. May 11, 2006) *affirmed by* 171 Cal. App. 4th 1549 (2009) (defendant's experts included medical doctor, FDA/labeling expert, consumption expert, toxicologist, and two experts regarding whether the chemical was naturally occurring); *ELF v. Beech-Nut Nutrition Corp.*, No. RG11597384, 2013 WL 5402373 (Cal. Super. Ct. July 31, 2013) *affirmed by* 235 Cal. App. 4th 307 (2015) (defendants used seven experts, including nutritional biochemist, toxicologists, and developmental nutritionist); *Dipirro v. J.C. Penny Company, Inc.*, San Francisco Superior Court Case No. 407150 (Feb. 9, 2005) (defendant presented four expert witnesses at trial: analytical chemist, two toxicologists, and marketing/human behavior expert), Addendum at Add-1; *Council for Education and Research on Toxics (CERT) v. Starbucks, et al.*, No. BC435759 (Los Angeles Superior Court) (defendants disclosed at least 13 experts in liability phases of the Proposition 65 coffee litigation), Addendum at Add-17.

1. Proposition 65's heavy burden of toxicology and risk assessment forces false and misleading speech

Many chemicals do not have an established "no significant risk level" ("NSRL"), so the defendant must establish one. *Compare* Cal. Code Regs. tit. 27, § 25705 (NSRLs for 273 chemicals) *with id.* § 25701(b) (613 cancer listings). Even when OEHHA establishes an NSRL, it often does not use the most

appropriate study or set of studies to do so. Thus, whether or not OEHHA has promulgated its own Proposition 65 "safe harbor" NSRL, defendants that do not wish to adopt false or misleading speech must significantly invest in expert opinions on toxicology and risk assessment in order to more accurately answer the question at what dose does the chemical at issue actually present a "known" risk to humans.

OEHHA's "risk analysis" is unduly conservative for a "known to cause" warning because it is "based on the most sensitive study deemed to be of sufficient quality." *Id*. § 25703(a)(3); 6-ER-1262, 66 (most sensitive animal study used in developing glyphosate NSRL; human evidence not used). For glyphosate, a defendant would face the expensive burden of putting forward all of the expert toxicology evidence concerning why hemangiosarcomas observed in mice treated with glyphosate, the data used for OEHHA's NSRL, are not the most appropriate data for predicting human cancer risk. *See e.g.*, *Williams*, *supra*, at 11[10] ("[T]he Expert Panel concludes that overall the evidence does not support the conclusion that glyphosate exposure results in an increased incidence of hemangiosarcoma in mice."); *see also* 6-ER-1284 (one of the State's Proposition 65 scientific experts, Carcinogen Identification Committee member and former OEHHA scientist Dr. Thomas McDonald, agreed that the hemangiosarcoma in mice is not appropriate for risk assessment).

To the best of our knowledge, OEHHA always uses the most conservative "linearized multistage model for extrapolation from high to low doses" for its Proposition 65 NSRLs, and does not consider whether a different model would be more appropriate. *See, e.g.*, Cal. Code Regs. tit 27, § 25703(a)(5), OEHHA FSR, NSRL for p-chloro-a,a,a-trifluorotoluene (Dec. 15, 2020) (linearized multistage model used for non-genotoxic chemical with no indication that OEHHA evaluated whether it was the best fit).[11] Thus, a defendant likely would also face the burden of putting forward evidence on the model that offers the best fit for the data, rather than the highly conservative linearized model used by OEHHA. *See* Lovell DP and Thomas G., *Quantitative risk assessment and the limitations of the linearized multistage model. Human & Experimental Toxicology*. 1996;15(2):87-104, at 101 ("conservative assumptions underlying the model"), Addendum at Add-30. USEPA, for example, offers a suite of 9 models to extrapolate from high animal doses to low doses; USEPA and other agencies commonly use a variety of models to extrapolate cancer risk from high doses. *See* USEPA, Benchmark Dose Software[12]; *see also* USEPA, 2019, 1,*3-Dichloropropene: report of the Cancer*

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[10] *See* Footnote 3.

[11] https://oehha.ca.gov/media/downloads/crnr/pcbtfnsrlfsorfinaltooal120220remediated.pdf

[12] https://www.epa.gov/bmds

Assessment Review Committee. Washington, DC, at 5, 44 (rejecting linearized multistage model).[13]

OEHHA NSRLs also conservatively avoid using a threshold model that is appropriate when the data indicate there is a dose below which no tumor increases occur. *See, e.g.*, OEHHA Initial Statement of Reasons ("ISOR"), NSRL, Trichloroacetic Acid, p. 4 & Table 1 (study used for the proposed NSRL showed a 20% *decrease* in liver tumors compared to controls at the low dose; yet, the highly conservative linearized model OEHHA used predicts a 5% or greater *increase* in liver tumors at a similarly low dose).[14]

Because these factors overstate actual risk and are expensive for defendants to address in proving their affirmative defense, defendants are systematically forced to provide safe harbor warnings, either before litigation or to settle litigation, that convey their products pose a cancer risk even though the science does not support doing so. In addition to being seriously burdensome for defendants, this is misleading and deepens the First Amendment problems.

[13] https://yosemite.epa.gov/sab/sabproduct.nsf/E035B3D665F05A5685258581003AFC3F/$File/EPA-HQ-OPP-2013-0154-0104.pdf

[14] https://oehha.ca.gov/media/downloads/crnr/trichloroaceticisor052220.pdf. Based on the data in ISOR, Table 1 and the same USEPA Benchmark Dose Software OEHHA used to determine the NSRL.

2. Proposition 65's heavy burden of exposure assessment forces false and misleading speech

Defendants in Proposition 65 litigation also face the burden of identifying the "reasonably anticipated rate of exposure for an individual to the given medium of exposure measured over a lifetime of seventy years." Cal. Code Regs. tit. 27, § 25721(c). A scientific exposure survey often is needed to identify this information. And an expert in exposure analysis or survey design, or both, normally is required. *See, e.g., Tri-Union Seafoods*, *supra*, 2006 WL 1544384 (defense expert testified about survey "he prepared and conducted in order to determine the average frequency of consumption of canned tuna by women of childbearing age in California"); *CERT v. Starbucks, et al.*, *supra*, Addendum at Add- 17 (disclosing Carolyn Scrafford, an exposure expert). Unlike most laws and regulations concerning food and consumer products, Proposition 65 does not communicate to companies how much of a regulated chemical may be in their product without a warning. Instead, Proposition 65 forces companies to undertake that expensive analysis themselves based on data they need to generate. Cal. Code Regs. tit. 27, § 25721.

3. Proposition 65's potentially astronomical penalties force false and misleading speech

Proposition 65 plaintiffs are quick to remind defendants of the up to $2,500 "per day for each violation" penalty. Cal. Health & Safety Code § 25249.7(b). The AG and private enforcers take the position that each person exposed to a

product without a warning is a separate violation. *See* March 12, 2007 AG Letter, Addendum at Add-48 ("sale of the potato chip would constitute one violation of the statute"). So, if a company sells 100,000 units of a product in California during the relevant period, which would not be uncommon, the potential penalty is $250 million. The plaintiff that recently sought warnings for acrylamide in coffee, for example, sought well over one *billion* dollars in penalties. *See* Plaintiff's Trial Brief Regarding the Determination of Civil Penalties for Violation of Proposition 65 (Aug. 11, 2017), *Starbucks, et al.*, *supra*, at 1-2, 10, Addendum at Add-54. Penalties at this level incentivize settlements even when the defendant believes it is 90-95% likely that it will prevail, because the magnitude of the potential loss for an unlikely outcome is so high.

Moreover, Proposition 65 is not a law where businesses can hope that the potential financial sting or warning obligations presented by a case will be mitigated by neutral public officials who may exercise reasonable enforcement discretion. The vast majority of Proposition 65 enforcement is by private plaintiffs, who pursue any and all potential litigation opportunities. In the three year time period from January 1, 2018 through the end of 2020, private plaintiffs issued 8,292 Proposition 65 60-Day notices of intent to sue one or more companies.[15] Parties settled 2,362 matters in that same time frame (842 were

[15] https://oag.ca.gov/prop65/60-day-notice-search

court-approved and 1,520 settled out of court).[16] In that same time period, the AG filed approximately nine[17] Proposition 65 cases and settled one.[18]

IV. Affirming the district court would not undermine appropriate public health messaging.

Although the First Amendment properly will prevent the State from enforcing Proposition 65 in circumstances where, like this one, the chemical at issue is not actually "known" to cause cancer, that will not endanger public safety. The USEPA has authority to place warnings on consumer and occupational pesticides that will keep the California public safe and informed. 7 U.S.C. §§ 136 *et seq.*, including § 136a(c)(5) and § 136j(2)(G). When appropriate, warnings accompanying a USEPA-approved label include, for example: a restricted use pesticide statement; a child hazard warning statement; hazard and precautionary statements; hazards to humans; environmental hazards; and worker protection labeling. *See generally* 40 C.F.R. Part 156; USEPA (2018) Label Review Manual, Chapter 3: General Labeling Requirements.[19]

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[16] https://oag.ca.gov/prop65/report/judgments-by-plaintiffs and https://oag.ca.gov/prop65/report/out-of-court-settlements

[17] Estimated using the Courthouse News Service (https://cnsplus.courthousenews.com/) and Bloomberg Law (https://www.bloomberglaw.com/product/blic/search/results/bb5ceae9d77cdcf1980c84e9d8b7547d) public filings databases.

[18] https://oag.ca.gov/prop65/annual-settlement-reports. We are not aware of any Proposition 65 AG settlements in 2020 and the AG has not described any on his website.

[19] https://www.epa.gov/sites/production/files/2018-04/documents/chap-03-mar-2018_1.pdf

Herbicide products also require state registrations issued by the California Department of Pesticide Regulation ("DPR") pursuant to the California Food & Agricultural Code. *See, e.g.*, Cal. Food & Ag. Code §§ 12824, 12825; Cal. Code Regs. tit. 3, § 6158. DPR's review criteria include acute toxic health effects, evidence of chronic health effects such as carcinogenicity, and potential for environmental damage. *Id*.

Likewise, California and the Federal Government have ample tools to regulate foods and consumer products based on laws other than Proposition 65.[20] And, California and other governments may themselves speak to the health issues of concern to them.[21]

[20] *See generally* Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*; 21 U.S.C. § 348; 21 C.F.R. Part 170; 21 U.S.C. §§ 331(a), 342, 343, 350g, 350h, and 350i; 21 C.F.R. Parts 117, 121; 21 U.S.C. § 343-1; 21 C.F.R. Parts 101, 111, and 112. The FDA and the Federal Trade Commission have overlapping jurisdiction over the advertising and promotional labeling of foods. *See* 21 U.S.C. § 343(a); 15 U.S.C. §§ 45, 52, and 55; 21 U.S.C. § 3501. The Federal Hazardous Substances Act requires warning labels on the immediate containers of hazardous household products. *See* 15 U.S.C. §§ 1261, *et. seq.*; 16 C.F.R. Part 1500.

[21] *See, e.g., Alerts, Advisories & Safety Information*, U.S. Food and Drug Administration, https://www.fda.gov/food/recalls-outbreaks-emergencies/alerts-advisories-safety-information#food.

CONCLUSION

For the reasons described, the district court's decision should be affirmed.

Dated: May 19, 2021

Respectfully submitted,

/s/ Gary M. Roberts
Gary M. Roberts
Sarah Ratcliffe Choi
DENTONS US LLP

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9th Cir. Case Number(s) 20-16758

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Signature: */s/ Gary M. Roberts* **Date:** May 19, 2021

ADDENDUM

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ORIGINAL

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SUPERIOR COURT OF THE STATE OF CALIFORNIA

COUNTY OF SAN FRANCISCO, UNLIMITED CIVIL JURISDICTION

MICHAEL DIPIRRO,

Plaintiff,

v.

J.C. PENNEY COMPANY, INC.; AND DOES 1 through 150, inclusive

Defendants.

Case No. 407150
(Consolidated with Case No. 407458)

Honorable A. James Robertson

TRIAL DEPT: 503

~~[PROPOSED]~~ STATEMENT OF DECISION Liability Phase
(California Rule Of Court 232)

MICHAEL DIPIRRO,

Plaintiff,

v.

MACY'S; AND DOES 1 through 150,

Defendants.

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STATEMENT OF THE CASE

I. DESCRIPTION OF TRIAL

On July 28, 2003, trial in the above-entitled matter commenced before the Honorable A. James Robertson II, sitting without a jury. Gregory M. Sheffer, Esq. and Clifford A. Chanler of Sheffer & Chanler LLP appeared for Plaintiff Michael DiPirro, and Jeffrey B. Margulies, Esq. and Rachel D. Stanger, Esq. of Parker, Milliken, Clark, O'Hara & Samuelian appeared for Defendants J.C. Penney Company, Inc. (hereafter "J.C. Penney") and Macy's West, Inc. (hereinafter "Macy's West"). Mary Harokopus, Esq. appeared pro hac vice for J.C. Penney. On September 8, 2003, Ann M. McGrath, Esq. of Parker, Milliken, Clark, O'Hara & Samuelian also appeared on behalf of Defendants.

The court trial lasted for 72 days. Opening statements were given on July 30, 2003. Presentation of Plaintiff's evidence was given on July 31 - August 21, 2003. Presentation of Defendants' evidence was given on August 26, September 8 - November 13, 2003. Plaintiff presented rebuttal evidence and closing arguments were made in court starting on November 18 through December 2, 2003. Thereafter, the parties submitted further written and oral argument at the Court's request by telephone on December 11 and 18, 2003. Further briefs and proposed statements of decision were submitted by the parties pursuant to a schedule established by the Court. The Court required written comments by each party directed to the submissions of the other party. The Court held a number of telephonic conference hearings concerning these matters in which there were further arguments. The matter was submitted for decision on April 28, 2004. A total of twenty-three witnesses testified at trial between July 31, 2003 and November 10, 2003. The Plaintiff presented eight witnesses during trial, which included two investigators,[1] one laboratory technician,[2] three experts,[3] one glassware manufacturer representative[4] and in-house counsel for J.C. Penney, Mary Harokopus.

[1] Russell Brimer, Dea Services investigator and Bernice Dea, owner of Dea Services.

[2] Hugh Dennis Dougherty, laboratory technician for Curtis & Tompkins laboratory.

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The Defendants presented sixteen witnesses, which included five buyers,[5] one glassware manufacturing representative,[6] one testing witness,[7] one cosmetic usage witness,[8] three in-house counsel witnesses,[9] four experts,[10] and the Plaintiff, Michael DiPirro.

In addition, during the course of trial, both Plaintiff and Defendants each brought a Motion For Judgment under C.C.P. 631.8. The Court declined to rule on both motions until submission of the case. Plaintiff also brought three motions to exclude witnesses Richard Brinkman, Christine Parker, Owen Jones and other percipient witnesses of each Defendant and two motions for sanctions based upon Defendants alleged failure to provide information regarding "knowledge" and failure to identify products. All such motions were denied due to a failure to demonstrate knowing violation of a prior court order. In addition, Plaintiff served trial discovery on Defendants in the form of special interrogatories and requests for production. Defendants objected to the discovery as untimely and improper. On July 30, 2003, the Court considered the objections and ruled that Defendants were only required to answer select, modified special interrogatories and requests for production.

During the trial, Plaintiff introduced 209 exhibits and Defendants introduced 218 exhibits.

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[3] Dr. David Robert Brown, toxicology expert; Michael Mazis, advertising and marketing expert; Dr. Barbara Callahan, toxicology expert.

[4] Soleiman Gabay, President of Gibson Overseas, Inc.

[5] Elizabeth Morello, Senior Vice President and General Merchandise Manager, Fragrances and Cosmetics for Macy's West; Jill Barr, buyer of cosmetics for Macy's West; Judy Strother, administrative assistant in the Tabletop division of J.C. Penney; Richard Brinkman, former Senior Buyer in the Tabletop Division of J.C. Penney; Christine Parker, Senior Buyer of cosmetics for J.C. Penney.

[6] Wayne Zitkus, manager of international business development for Libbey, Inc., manufacturer of painted glassware.

[7] Owen Jones, former Product Safety Coordinator for the Retail Testing Laboratory at J.C. Penney.

[8] John Voda, Director of Research at Pragmatic Research responsible for the CTFA study regarding cosmetic usage.

[9] Christine Brandt, in-house counsel for Macy's West; Mary Harokopus, in-house counsel for J.C. Penney; Susan Witt, paralegal for J.C. Penney.

[10] Dr. Carla Kagel, analytical chemistry expert; Dr. Michael Lakin, toxicology expert; Dr. James Embree, toxicology expert; Dr. Wayne Stewart, false advertising expert.

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The parties stipulated and agreed that, should it be necessary to decide any issues concerning remedy, those issues would be bifurcated for separate trial after a decision is reached on the liability phase of the case. Pursuant to this stipulation, the Court ordered the case bifurcated.

II. SUMMARY OF STATEMENT OF DECISION

For the reasons set forth in this tentative decision, the Court finds as follows:

1. Plaintiff has proved that J.C. Penney and Macy's West caused exposures to lead (a chemical listed pursuant to the Health and Safety Code) through their sale of cosmetic products and further finds that J.C. Penney caused exposure to lead through their sale of painted glassware.

2. With respect to the sale of the cosmetic products, the Court finds that J.C. Penney and Macy's West did not knowingly cause any exposure to lead in cosmetics with the sale of such product because they were unaware such products contained lead. Accordingly, the Court finds J.C. Penney and Macy's West have no liability for the sale of such products under the Health and Safety Code. In connection with this finding of no liability, the Court did determine that the notice issued by Plaintiff gave Plaintiff standing so that the Court could make its finding of non-liability. The Court further concluded that the doctrine of estoppel does not foreclose Plaintiff for asserting claims as to cosmetic products.

3. With respect to painted glassware, the Court finds that J.C. Penney knowingly caused an exposure to lead by selling glassware painted with lead paint because J.C. Penney was aware the paint on the exterior of the glasses contained lead and J.C. Penney was aware customers would touch the lead paint in the normal course of drinking from the glasses. Accordingly Plaintiff has established liability for a knowing exposure. Since the glassware was intentionally sold and not accidentally distributed, the Court finds that J.C. Penney acted intentionally in exposing customers to the lead in the glassware. Therefore, J.C. Penney is liable for any sale of such glassware as may have occurred. In making this finding, the Court concludes Plaintiff's notice was sufficient to

B. Defendants' Experts

1. Carla Kagel, Ph.D.

Dr. Kagel is an analytical chemist. She testified that the EPA Method 3050B (Exhibit E, solid digestion for metals), NIOSH Method 9100 (Exhibit D, surface lead wipe), and ASTM Method C927 (Exhibit C, lip and rim immersion in acetic acid) test methods used by Plaintiff were neither validated nor generally accepted for the purpose of showing exposure to lead from cosmetics and glassware, and she believed that blood lead testing was the only way to establish actual exposure to lead. Moreover, these methods tested for total lead, including all organic and inorganic compounds, as well as metallic (elemental) lead. Dr. Kagel did acknowledge that blood lead levels can detect wholesale changes in blood from lead exposure, but cannot differentiate the source of exposure from the myriad of potential exposures suffered by any given person – especially since the majority of the lead is going to be absorbed by bone and soft tissue. (Kagel Trial Testimony 9/9/03.) Dr. Kagel acknowledged that blood is not the "medium" to which any individual is ever exposed and would not be appropriate to identify the lead concentration in any given "medium" of exposure such as air, water, soil, food and and/or consumer products. (Kagel Trial Testimony 9/9/03.)

Dr. Kagel did not perform her own tests on any of the products, but reviewed the testing documents and testimony produced by Plaintiff. She testified that Plaintiff had not followed a sampling plan as required by Method 3050B, which made it impossible to assess the applicability of the results to other, non-tested products. Dr. Kagel testified that the 3050B digestion tests of cosmetics performed by Curtis & Tompkins were in the range of background lead (i.e., lead results of 5 ppm can be due to lead in the environment, and not necessarily in the cosmetics). Dr. Kagel testified that she had no evidence to suggest that there was contamination of the products tested by Curtis & Tompkins for Plaintiff. (Kagel Trial Testimony 9/9/03.) Dr. Kagel was not familiar with each product's chain of custody or the products' packaging. (Kagel Trial Testimony 9/9/03.) Dr. Kagel testified that the control blanks data she reviewed—laboratory analyzed for purposes of identifying

contamination or improper machinery calibration—were all within the acceptable range and showed no indication of any contamination. (Kagel Trial Testimony 9/8/03, 9/9/03.) The results were very close to the reporting limits for the tests, and those limits were unlikely to be accurate. (Kagel Trial Testimony 9/8/03 and 9/9/03.) As an analytical chemist, she testified that she relies upon validation data from a laboratory as indicia of reliability of the reported test results, and the lack of any validation data in the materials produced by Plaintiff made it impossible for her to rule out laboratory error or other causes of the reported low levels of lead in the cosmetics tested by Plaintiff. Dr. Kagel testified that she charges her clients for providing reports in a similar fashion as Curtis & Thompkins; without the "data validation" package. Dr. Kagel stated that this style of report is absolutely appropriate and she would not ordinarily prepare a data validation package herself unless specifically requested by the client, for an additional fee. (Kagel Trial Testimony 9/8-9/03).

Dr. Kagel believed that the amount of lead that would be released by the 3050B hot acid digestion exceeded the amount of lead that would be released from a cosmetic that was on the skin or in the stomach of a user, given the nature of the digestion. However, Dr. Kagel is not a toxicologist and did not offer an opinion on the way the cosmetic products might react with an individual during an instance of exposure. Although she did not have any first-hand observations of the testing, in her opinion, the types of problems associated with Plaintiff's tests and the results of those tests would be likely to overestimate the amount of lead in the cosmetics. Dr. Kagel did not examine any additional, independent testing data from the manufacturers of the cosmetics.

Dr. Kagel testified that the NIOSH 9100 wipe tests performed by Plaintiff were within the range of background (5 µg/wipe). The glasses had not been washed before they were wiped, and based on the documents from the laboratory, one cannot determine if the lead came from the paint on the glass or an external source, since lead is ubiquitous in the environment, including air and water. Dr. Kagel did not consider the equivalent lead concentrations for washed glassware. Also, the 9100 method is not validated to show

release of metals from a surface. Therefore, she opined that the results of Plaintiff's wipe tests did not show that lead was released from the painted surface of the glassware. The NIOSH 9100 method is accepted and adopted for use by the Federal government and was created and issued for the purpose of showing lead on the surface of objects. U.S. EPA and the CPSC expressly adopted NIOSH 9100 for demonstrating the leach of lead from surfaces (i.e. painted walls, mini-blinds, playground equipment, etc.). (Exhibits 135, 136).

Dr. Kagel testified that the C927 immersion tests performed by Plaintiff are subjective, and subject to potential laboratory error due to improper equipment or technique. Curtis & Tompkins modified the method by marking the 20 mm line with tape, and did not validate that modification to show that the results were accurate. It also modified the method by immersing glassware beyond the 20 mm line. However, Dr. Kagel did not know exactly the steps taken by Curtis & Thompkins in performing the glassware tests and Dr. Kagel did not identify specific laboratory error in the testing of the glassware. The results of a C927 test do not necessarily bear any relationship to the amount of lead that could reasonably be released from a glass through normal use. Dr. Kagel did not study the type of beverages that might be used in a glass, including juice or wine, nor did she study Dr. Brown's wash and wipe test.

2. Michael L. Lakin, Ph.D., DABT

Dr. Lakin is a board-certified toxicologist, who has extensive experience in risk assessment and Proposition 65 exposure assessments. Dr. Lakin testified regarding exposure to lead from cosmetics. Dr. Lakin testified that Plaintiff had not shown an exposure to lead from cosmetics. First, he testified that the 3050B Method is not specific to the lead listed under Proposition 65, which is limited to the OSHA listing of metallic lead, inorganic lead, and organic lead soaps, and does not itself meet the requirements of 22 Cal. Code Regs. § 12901. Dr. Lakin acknowledged the FSOR for § 12805 providing the MADL for lead does not reference any limitation on what constitutes "lead", nor does the listing of the chemical itself. Dr. Lakin admitted that compounds of lead, inorganic and organic alike, contain the same elemental lead, and breakdown to the same elemental

lead. Second, any lead that is in the cosmetic would be in a matrix, and no tests had been performed to show that the lead was available to penetrate the skin or be absorbed in the stomach. Dr. Lakin did not do any research into the chemicals in the lipstick formulation or how those chemicals bonded together to otherwise for a "matrix." Third, lead on the skin is not an exposure to lead from a toxicological perspective, because there has been no demonstration that the lead is or can penetrate the skin, and "contact" with a boundary to a toxicologist (as the word "contact" is used in 22 Cal. Code Regs. § 12102 (i)) means communication with the boundary). In order for lead to cause reproductive effects it must enter the bloodstream, and the only validated and generally accepted method of demonstrating exposure to lead is by measuring blood lead. Dr. Lakin based his opinion of dermal absorption of inorganic lead on dermal absorption factors utilized in government "lead spread models", on a research paper published in 1988, and the EPA dermal absorption guidance document. As for blood lead levels, they do not distinguish between "old lead" that is being released from bone and "new lead." In Dr. Lakin's opinion, there was no evidence from which one could determine that any lead in cosmetics was capable of crossing, or in fact did cross, the skin, or was ingested or absorbed through the ocular area. Dr. Lakin had not studied the structure of the eye with respect to absorption of lead. Dr Lakin acknowledged that the conjeunctiva, or inner eyelid, was highly vascularized and had no protective lipid layer to withstand absorption of the lead in makeup. (Lakin Trial Testimony 9/28-9/30/03.) Dr. Lakin also admitted that the naso-lacrimal gland functioned like a giant drain to bring materials contacting the eye or eyelid down into the nasal passage, mouth and stomach—all the way along another highly vascularized wall of easily penetrable epithelial cells. (Lakin Trial Testimony 9/28-9/30/03.)

Dr. Lakin testified that, assuming the lead tested by Plaintiff was the chemical listed under Proposition 65, and that Plaintiff's tests data in fact showed lead (i.e., was reliable), the amount of lead in the cosmetics did not exceed the level that required a warning under Proposition 65. Dr. Lakin performed a theoretical upper bounding estimate

("TUBE") to assess the potential magnitude of the exposure. Following the safe harbor approach of 22 Cal. Code Regs. § 12821, as explained in the Final Statement of Reasons (FSR) for Article 8 of the Proposition 65 implementing regulations (Exhibit G), he compared the reasonably anticipated rate of intake or exposure, (based on product usage data and lead content) with the Maximum Allowable Daily Level (MADL) of 0.5 µg /day for lead established by 22 Cal. Code Regs. § 12805(b). He relied upon Plaintiff's test data for the amount of lead in cosmetics, which he believed was likely to overestimate actual exposure due to the acid digestion. He relied, based on guidance in § 12821, upon product usage information from the EPA Exposure Factors Handbook (Exhibit 4Ms), the CTFA Study of lipstick usage (Exhibits 40s and 5Gs), and the European Union Notes of Guidance for Testing of Cosmetics Ingredients for Their Safety Evaluation (Exhibit 4Ns), to estimate the amount of product used by average users of the cosmetic products.

Based on these data, the amount of lead placed on the skin of the user for any individual product within a cosmetic kit, and for a worst-case use of all tested products in any cosmetic kit, did not exceed 0.5 µg/day, whether the user was an average user, or in the upper 90th percentile of all users. Dr. Lakin testified that it would not be proper to include all exposures to lead from the various components of the cosmetic kits in one exposure assessment, because the products were not necessarily used together by the average user; however, including all of the products did not cause the amount of lead applied to the skin to exceed 0.5 µg/day.

Dr. Lakin testified that standard toxicological exposure assessment principles required the analysis of actual absorption of lead through the skin and stomach. These principles were consistent with Proposition 65's implementing regulations as described in the "pattern and duration of exposure" in § 12821 and with guidance in the Final Statement of Reasons that indicated it was appropriate for absorption to be considered in determining whether an exposure posed no observable effect within the meaning of Proposition 65. Dr. Lakin testified that it would not be inappropriate to apply absorption to different routes of exposure to lead when using the 0.5 µg/day MADL, as that MADL

had been developed based on inhalation data only, and lead was absorbed very poorly, if at all, by dermal contact, and at ranges of 6-10% by ingestion under average conditions, compared with very efficient absorption of lead when inhaled. Dr. Lakin testified that there was no prohibition in the regulations or Final Statement of Reasons against applying route-specific absorption data, and that the California Environmental Protection Agency Office of Health Hazard Assessment (OEHHA) had changed its practices to do so when adopting MADLs in light of a recommendation from a peer-review of its risk assessment practices in the mid-1990s (approximately 10 years after the lead MADL had been adopted). When Dr. Lakin included the standard absorption factors used by Cal/EPA and federal EPA, the amount of lead exposure he calculated from the cosmetics was at least 1000 times below the MADL for all products within a kit.

Dr. Lakin did not test any cosmetic products, as the Plaintiff's test results were orders of magnitude below the warning level, and there was no reason to believe that further testing would result in significantly elevated exposures. Dr. Lakin rejected the after-the-fact argument that Plaintiff's test results were inaccurate and underestimated the total amount of lead in the products.

Dr. Lakin testified that exposure to lead is not properly assessed on a one-day basis, because it is not a teratogen. Toxicologists, and California state agencies, typically assess lead exposure on a 30-day average exposure, because the reproductive effects for which it is listed are based on chronic exposure. For purposes of his assessment, he assumed that the exposures he calculated were occurring every day. Dr. Lakin testified that the amount of lead to which a women would be exposed would not be detectable in her blood. He also testified that the products posed no danger to users from any lead that was contained in them.

3. James W. Embree, Ph.D., DABT

Dr. Embree is a board-certified toxicologist, who has extensive experience in risk assessment and Proposition 65 exposure assessments. Dr. Embree testified regarding exposure to lead from painted glassware. Dr. Embree testified that Plaintiff had not

shown an exposure to lead from cosmetics, because Plaintiff had not tested for the specific listed chemical in the specific medium, as is required under 22 Cal. Code Regs. § 12901. Dr. Embree performed some testing of paint on glassware, but it did not change his opinion that Plaintiff did not test for the listed chemical for the specific medium.

Dr. Embree testified that the ASTM C927 Method does not show an exposure to lead from glassware, as it is not validated to do so, and the method specifically states that it does not represent actual conditions of use. Dr. Embree acknowledged FDA comment that the C927 voluntary testing program "will ensure that the public is not presented with any significant health risk due to lead . . . that may leach from decorated glass tumblers." (Ex. 4D, p. 58633.) Although he did not observe the Curtis & Tompkins testing for Plaintiff, his own pilot testing with acetic acid led him to believe that there were potential problems with the tests performed by Curtis & Tompkins. These potential problems included the improper equipment used to perform the test and the possibility of contamination or disturbance of the samples while the test was being performed. His own pilot testing with artificial saliva led him to conclude that acetic acid immersion for 24 hours did not provide any realistic assessment of whether lead leached from the glassware under normal conditions of use. Dr. Embree admits his protocol is experimental and does not establish an approved scientific methodology for lead leaching from paint on a glass. Dr. Embree did not take account of the possible acidity of the beverage being consumed on the exterior rim, which may have a similar acidity to the leaching solution used in the C927 Method. The use of the C927 Method did not meet § 12901 because it is not specific to the listed lead, but tests for all lead, and the medium tested is acetic acid, which is not the medium to which the user is exposed.

Dr. Embree acknowledged that the NIOSH 9100 wipe test is a federally created standard adopted for identifying the surface presence of chemicals on an object. However, Dr. Embree testified that the NIOSH 9100 wipe tests did not show an exposure to lead from glassware for several reasons. First, the method is not validated to show exposure to lead leaching from a surface, as it is only validated to show environmental

contamination of lead. Since Plaintiff had not washed the glasses before testing them, there was no basis to conclude that the lead in the tests came from the paint on the glass. Second, the method is not specific for the listed lead, but tests for all lead, and the medium tested is the lead itself on the surface of the glass.

In Dr. Embree's opinion, from a toxicological perspective, the medium of concern is that which carries the chemical to the body. Thus, the media to which the user was exposed to lead that might be released from the painted glass surface could be the saliva (in the case of direct contact) or the object to which the lead was supposedly transferred, such as a piece of bread (in the case of indirect contact). FSOR for 22 CCR § 12821 defines the "medium" as a certain type of food or a consumer product, but that the exposure from a given medium will depend upon the medium, its anticipated use and other circumstances. (Exhibit G, pg. 83). Dr. Embree testified that the medium at issue in this case is not the product, because the user is not actually ingesting the product. Because there was no method that met the requirements of § 12901, in his opinion there was no showing of exposure to lead from the products. While acknowledging that NIOSH 9100 and ASTM C927 are adopted by both State and Federal governments, Dr. Embree, as with Dr. Lakin, testified that the only validated and generally accepted method of demonstrating exposure to lead is by measuring blood lead.

Dr. Embree testified that, even assuming that the tests showed the listed chemical, because the various potential media of exposure had not been identified or tested, there was no method that met the requirements of § 12901 that would allow for the quantification of the amount of lead to which average users were exposed. If he was forced to accept Plaintiffs tests as demonstrating an exposure (thus meeting § 12901), then he opined, in his professional judgment, that the user would only ingest approximately 5% of the total amount wiped off of a glass with the modified NIOSH 9100 methodology. Dr. Embree agreed that this 5% "guesstimate" was just a personal, professional judgment. This judgment was not made to any reasonable degree of scientific validity or certainty; not based upon any scientific study or principle. Dr. Embree did not analyze the hand-to-

mouth ingestion and he rejected both the CPSC's 50% figure from the mini-blinds experiment and the CPSC's 43% figure from the playground equipment investigation, as well as the EPA's Exposure Factors Handbook's reported comparison of the hand-to-mouth ingestion rates between children and adults of 50%. In analyzing his modified test, Dr. Embree concluded that not all lead transferred to the hands would ultimately be ingested, and then premised his quantification estimate on several grounds including, (a) the pad used to wipe the glass was more abrasive than a finger; (b) fingers of the user would not contact the entire surface of the decoration, in contrast to the wipe, which was intended to cover the entire surface area (Dr. Embree did no investigation into how a normal user would use the glass, where they might contact it, whether any contact might involve rubbing the surface of the paint, the length of duration of the contact or the temperature and content of the glass.); (c) the handling of the product when it was used by the consumer; and (d) any lead transferred from the glass to the fingers could remain on the fingers, be transferred to an object and never enter the mouth, be transferred back to the glass, or be transferred directly or indirectly to the mouth.

In Dr. Embree's opinion, any glass with wipe test results of 10 µg/wipe would meet the 0.5 µg/day MADL. The estimate did not take into account any absorption of lead from the digestive tract; however, Dr. Embree testified that the relatively poor absorption of insoluble inorganic lead in the digestive tract would decrease the actual exposure to the user by 90%, based on data for such lead in the Agency For Toxic Substances ATSDR Toxicological Profile for lead. Dr. Embree had no specific information on what species of lead was present in the paint. He also had no information on solubility, except that he believed that the lead was inorganic and soluble because the glass would be washed before use. Dr. Embree testified that the use of absorption data was a principle of toxicological risk assessment, and was specifically identified as appropriate under the FSR for Article 8, including for ingestion of lead. As with Dr. Lakin, Dr. Embree testified that it would not be inappropriate to apply absorption to different routes of exposure to lead when using the 0.5 µg/day MADL, and there was no

prohibition in the regulations or Final Statement of Reasons against applying route-specific absorption data to the MADL. When applying this standard absorption factor, any wipe result of 100 µg or less would not exceed the 0.5 µg/day MADL.

Dr. Embree did not average a user's exposure over multiple days, although he believed it would be appropriate to do so for the purposes of chronic exposure analysis to lead. For purposes of his assessment, he assumed that the exposures he calculated were occurring every day. He also testified that, assuming exposure to the amount of lead in a wipe test, such exposure would not be detectable in the bloodstream of the user. He also testified that the products posed no danger to users from any lead that was contained in them.

4. David Stewart, Ph.D.

Dr. Stewart is a Professor of Marketing, and Deputy Dean of the Marshall School of Business, at the University of Southern California. Dr. Stewart testified that whether an omission is material depends on whether conveying the information will change the reasonable consumer's behavior. He testified that studies suggest that consumers don't think in terms of levels of chemicals, but is this a safe product, and should I exercise caution? Consumers look to experts to set standards in certain situations. In Dr. Stewart's opinion, it is not misleading to not warn about exposures to chemicals that are not potentially harmful. And, in the absence of any proof that products are potentially dangerous, the presence of lead is not "material" to an ordinary consumer, and it is therefore not misleading to omit identification of lead in the product. (Stewart Trial Testimony 10/7/03).

As he understands that lead is ubiquitous in the environment, Dr. Stewart testified that there are potential adverse impacts from Plaintiff's disclosure theory. Warnings about lead in non-harmful amounts may deluge consumers and drown out important warnings. Warnings may cause consumers to forego benefits from presence of lead (e.g., certain colors in glassware) without any increase in safety. A warning in the

circumstances of this case is potentially misleading to consumers, given the lack of potential harm from the products, and these other factors.

Dr. Stewart testified that it would be inappropriate to determine the need for warnings based on the aggregate risk posed by all of the products within a kit, as opposed to the individual products. Manufacturers typically bundle products together because consumers are likely to use those products together, but if the individual products are dangerous only in combination, the activity that needs to be addressed is the lifestyle choice of the user, not the way in which the products are packaged. Warnings on "kits" that are based on aggregation of risk from individual products will drive consumers to the same products separately-sold and individually-packaged, and will create no health benefit, because the consumers are subject to the same risk from the aggregate use of the individual products.

Dr. Stewart did not generally know whether the majority of the cosmetic kits contained components that were available for individual sale. Dr. Stewart acknowledged that B&P Code § 17500 does not concern itself with potential adverse impacts, only whether the consumer is likely to be misled. Dr. Stewart agreed that the relevant standard is whether the omitted information would affect a consumer's decision to purchase the product.

V. EVENTS AFTER THE FILING OF THE NOTICES AND COMPLAINTS

A. Macy's West's Actions Following Receipt of Notice for Cosmetics

On November 20, 2001, Plaintiff served Macy's West with a 60-Day Notice of alleged violation of Proposition 65 for selling certain cosmetic kits containing lead without a clear and reasonable warning. *See* Exhibit 91. The notice specifically identified the products at issue as "COSMETIC KITS" and further referenced, as specific examples, "The Color Institute Spring Beauty" and "The Color Institute Color Ensemble" cosmetic kits, manufactured by Markwins. The notice identified Markwins as the "manufacturer" of the products at issue.

from this approach include drowning out other important warnings and causing consumers to forego benefits of products (or even benefits of lead in products) without any increase in safety.

VII. CONCLUSION (Liability Phase)

For the foregoing reasons, the Court finds no violation of Proposition 65 for both Defendants for their sale of cosmetic products and no violation for both Defendants for false advertising. The Court does not find J.C. Penney to have violated Proposition 65 for any sales of painted glassware which may have occurred.

~~In any event, Defendants' counsel shall prepare, serve, and submit within twenty(20) days a proposed Judgment pursuant to the terms of this Tentative Decision.~~

DATED: Feb 9, 2005

A. James Robertson, II
Judge of the Superior Court

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SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES, CENTRAL CIVIL WEST

COUNCIL FOR EDUCATION AND RESEARCH ON TOXICS, a California corporation, acting as a private attorney general in the public interest; Plaintiff, vs. STARBUCKS CORPORATION, a Washington corporation; et al., Defendants.	CASE NO. BC435759 Consolidated with Case No. BC461182 *Assigned to the Honorable Elihu Berle, Dept. 323* **JOINT WITNESS LIST FOR PHASE 2 TRIAL** TRIAL DATE: September 5, 2017 TIME: 9:00 a.m. DEPT: 323

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TO THE COURT, TO DEFENDANTS, AND TO THEIR ATTORNEYS OF RECORD:

The parties hereby submit their Joint Witness List for the Phase 2 trial.

DATED: September 7, 2017

METZGER LAW GROUP
A Professional Law Corporation

RAPHAEL METZGER, ESQ.
SCOTT P. BRUST, ESQ.
Attorneys for Plaintiff
COUNCIL FOR EDUCATION AND
RESEARCH ON TOXICS ("CERT")

CERT v. Starbucks, et al.

Joint Witness List

Name	Description	Live/Transcript	Subject of Testimony	Time (Direct)	Time (Cross)
Abbott, Michelle R	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Abdollah, Michelle	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Adle, Terri	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Aguilar, Alberto	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Alam, Sm D	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Alexander, Dominik	Defendant Expert	Live	Epidemiology of coffee and acrylamide in coffee, with focus on non-cancer health effects and developments in cancer epiemiology since the 2014 conclusion of the Phase I trial, and in rebuttal to Plaintiff's experts.	3	3
Alferez, Nazareth	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Allen, David	Percipient Witness (Eight O'Clock Coffee)	Live/Transcript	Company-specific issues related to remedies and civil penalties	1	N/A
Alvarado-poblete, Stephanie K	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Anderson, Kevin	Percipient Witness Dunkin' Brands, Inc.	Live	Senior marketing distribution coordinator; marketing communications, new store openings.	1	0.5
Apuzzo, Joseph	Percipient Witness (Regal Commodities)	Live/Transcript	Company-specific issues related to remedies and civil penalties	1	N/A
Arredondo, Luis	Percipient Witness BP West Coast Products LLC	Live	*ampm* franchise structure and relationships, and placement and posting of Proposition 65 warning signs.	1	0.5
Arvizo, Gabriel	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Atkinson, Ben	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	1.5	0.5

CERT v. Starbucks, et al.

Joint Witness List

Name	Description	Live/Transcript	Subject of Testimony	Time (Direct)	Time (Cross)
Boatner, Kenneth	Person Most Knowledgeable / Percipient Witness (Ralphs Grocery Company; The Kroger Co.)	Live/Transcript	Company-specific issues related to remedies and penalties (e.g., sales, warnings, agreements with suppliers/ roasters, financials). Private label products	2.5	1
Boffetta, Paolo	Defense expert	Transcript	Coffee cancer epidemiology	0	N/A
Bomann, Heather E	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Boyer, Pamela	Percipient Witness (Quarter G Inc.)	Live/Transcript	Company-specific issues related to remedies and civil penalties	1	N/A
Boyle, John	Percipient Witness (Kauai Coffee Company, LLC / Massimo Zanetti Beverage USA, Inc.)	Live/Transcript	Company-specific issues related to remedies and civil penalties	1	N/A
Brautbar, Nachman	Plaintiff expert	Live	Coffee chronic disease effects	6	3
Bredt, Sean	Percipient Witness (Mother Parkers Tea & Coffee, Inc.)	Transcript	Company-specific issues related to remedies and civil penalties	N/A	N/A
Bridges, Jeff	Percipient Witness (Melitta U.S.A., Inc.)	Live	Company-specific issues related to remedies and civil penalties	1	0.5
Brouhard, Kristina	Percipient Witness (Peerless Coffee Company, Inc. dba Adam's Organic Coffees)	Live	Company-specific issues related to remedies and civil penalties	1	0.5
Brown, Graeme	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	1.5	0.5
Brown, Jamaal	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Buchanan, Brett	Percipient Witness (Starbucks Corporation)	Live/Transcript	Company-specific issues related to remedies and civil penalties	1	N/A

CERT v. Starbucks, et al.

Joint Witness List

Name	Description	Live/Transcript	Subject of Testimony	Time (Direct)	Time (Cross)
Gruver, Sean C	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Guevara, Tito	Percipient Witness BP West Coast Products LLC	Live	*ampm* franchise structure and relationships, and placement and posting of Proposition 65 warning signs.	1	0.5
Gutierrez, Hugo	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Gutwein, Cary	Percipient Witness (Copper Moon Coffee)	Live/Transcript	Company-specific issues related to remedies and civil penalties	1	N/A
Hailey, Shane R	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Hall, Ann	Percipient Witness (Coffee Roasters of Arizona, Inc.)	Live/Transcript	Company-specific issues related to remedies and civil penalties	1	N/A
Hall, Steven	Defendant Expert	Live	Proposition 65 warning signs.	4	1
Halverson, William	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	1.5	0.5
Hannon, Chris T	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Harding, John	Employee of Metzger Law Group	Live	Pre-suit survey of warnings	0.5	0.25
Hasheminejad, Kia M	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Hauptman, Jonathan E	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Hayden, Don J	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Haynes, Nancy	Percipient Witness (Napa Valley Coffee Roasting Company, Inc.)	Live	Company-specific issues related to remedies and civil penalties	1	0.5
Hayth, Stephen L	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Hepler, Rebecca	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25

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Joint Witness List

Name	Description	Live/Transcript	Subject of Testimony	Time (Direct)	Time (Cross)
Heuer, Andrea J	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Hlywka, Jason	Percipient Witness (Kraft Heinz Foods Company)	Live/Transcript	Company-specific issues related to remedies and civil penalties	1	N/A
Hollander, Kenneth	Defendant Expert	Live	Brewed coffee consumption by self-serve customers.	2	1
Holmberg, Jennifer	Percipient Witness Dunkin' Brands, Inc.	Live	Senior manager new business development; sales data, channel sales.	0.5	0.25
Holt, Arnie	Percipient Witness (Caffe Calabria Coffee Roasting Company, Inc.)	Live	Company-specific issues related to remedies and civil penalties	1	0.5
Hooks, Marcus S	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Hower, Norman	Percipient Witness 7-Eleven, Inc.	Live	Corporate representative, corporate business model, and corporate health and safety policies	2	1
Huff, James	Plaintiff expert (testified in Phase 1)	Live	Acrylamide/coffee cancer bioassays (only if defense expert depositions are re-opened)	2	
Hughes, Liam	Percipient Witness (Kerry Inc.)	Live/Transcript	Company-specific issues related to sales, remedies and civil penalties	1	N/A
Hunter, Ashlene	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Huynh, Karen	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Iacob, Ovidiu N	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Infante, Peter	Plaintiff expert	Live	Coffee cancer epidemiology	8	4
Isais, John	Percipient Witness (International Coffee & Tea, LLC dba Coffee Bean & Tea Leaf)	Live	Company-specific issues related to remedies and civil penalties	1	0.5
Jacobsen, Kurt	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
James, Jack	Plaintiff expert	Live	Cardio, cognitive, develop. effects	8	4

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Name	Description	Live/Transcript	Subject of Testimony	Time (Direct)	Time (Cross)
Kessler, David	Defendant Expert	Live	The appropriate regulatory framework for setting an alternative significant risk level (ASRL) supported by "sound considerations of public health" for acrylamide in coffee, and in rebuttal to Plaintiff's experts.	3	6
Ketch, Jonathan	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Khogyani, Ahmad N	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Kip, Sharon	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Kiper, Creighton	PMK of Wal-Mart	Transcript	Wal-Mart sales and warnings		N/A
Knott, Nancy	Percipient Witness BP West Coast Products LLC	Live	*ampm* franchise structure and relationships, and placement and posting of Proposition 65 warning signs.	1	0.5
Knox, Kia	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	1.5	0.5
Kruckner, Raymond	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	1.5	0.5
Kugler, Fritz	Percipient Witness (Zavida Coffee Company Inc.)	Live/Transcript	Company-specific issues related to remedies and civil penalties	1	N/A
Kwasiborski, Christophe R	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Kwasigroch, Mark	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Lammers, Tammi	Stater Bros. Markets employee	Live	Company sales data	1	0.5
Lankford, Timothy M	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Larson, Brent E	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Layon, Mindy	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25

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Name	Description	Live/Transcript	Subject of Testimony	Time (Direct)	Time (Cross)
Puritsky, Nicole A	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Quam-Wickham, Nancy	Percipient Witness CERT	Live/Transcript	CERT Officer; standing, public interest, penalties, warnings, notice/knowledge	1	1
Quazi, Junnun	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Quier, Laurence	Percipient Witness (Kauai Coffee Company, LLC / Massimo Zanetti Beverage USA, Inc.)	Live	Company-specific issues related to remedies and civil penalties	1	0.5
Ramirez, Maria V	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Rappaport, Steven	Plaintiff expert (testified in Phase 1)	Live	Exposure assessment, DNA adducts (only if defense expert depositions are re-opened)	2	
Rasmussen, James D	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Rauschenberger, Robert	Defendant Expert	Live	Clear and reasonable warnings in the event that the Court finds that Proposition 65 warnings are required for coffee.	2	1
Razo, Jason	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Real, Jason	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Reed, Jeddy	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	1.5	0.5
Regus, Justin	Defendant Expert	Live	Historical unit sales data during relevant time periods for BP West Coast Products LLC and 7-Eleven, Inc.	3	1
Reivitis, James	Percipient witness/photographer	Live	Photographs taken of stores	2	
Reyes, Jonathan C	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Rhee, Mike	Percipient Witness Dunkin' Brands, Inc.	Live	Operations manager; franchisee relations; placement and posting of warning signs.	0.5	0.25

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Name	Description	Live/Transcript	Subject of Testimony	Time (Direct)	Time (Cross)
Rhomberg, Lorenz	Defendant Expert	Live	Risk assessment, including but not limited to the appropriate ASRL for acyrlamide in coffee, and in rebuttal to Plaintiff's experts.	3	2
Richardson, Derek R	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Riley, Patricia R	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Rillo, Sixto	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Ristenpart, William	Defendant Expert	Live	Formation of acrylamide in coffee as a result of roasting necessary to render coffee palatable, and in rebuttal to Plaintiff's experts.	3	4
Rivera, Gilbert A	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Robinson, John W. III	Percipient Witness (S & D Coffee, Inc.)	Live	Company-specific issues related to remedies and civil penalties	1	0.5
Rogers, James D.	Percipient Witness (JBR, Inc. dba Rogers Family Company)	Live	Company-specific issues related to remedies and civil penalties	1	1
Rogers, Jennifer	Percipient Witness (Mayorga Organics, LLC)	Live	Company-specific issues related to remedies and civil penalties	1	0.5
Rogers, Michael	Percipient Witness (EDW Apffel Co.)	Live	Company-specific issues related to remedies and civil penalties	1	1
Romano, Mark	Percipient Witness (illy Caffe North America, Inc.)	Live/Transcript	Company-specific issues related to remedies and civil penalties	1	N/A
Romero, Mary	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Rosas, Jesus	PMK of 3rd Party M. Block & Sons	Transcript	delivery of Keurig coffee to California		N/A
Ross, David	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Ruby, Amelia	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25

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Name	Description	Live/Transcript	Subject of Testimony	Time (Direct)	Time (Cross)
Schaffer, Ryan	Percipient Witness Dunkin' Brands, Inc.	Live	Legal counsel; corporate structure of DBI, licensing and franchising relationships.	1	0.5
Scheumann, Roger	Percipient Witness (Quartermaine Coffee Roasters)	Live/Transcript	Company-specific issues related to remedies and civil penalties	1	N/A
Schinmann, Kevin	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	1.5	0.5
Schnell, Bruce A	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Schwalen, Christophe L	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Scollans, Mark	Percipient Witness BP West Coast Products LLC	Live	*ampm* franchise structure and relationships, beverage safety, and placement and posting of Proposition 65 warning signs.	3	1
Scrafford, Carolyn	Defendant Expert	Live	Average rate of exposure to acrylamide for the avergae consumer of coffee, and in rebuttal to Plaintiff's experts.	3	2.5
Sebastian, Paul R	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Seiple, James	Percipient Witness (Safeway, Inc. and Albertson's LLC)	Live/Transcript	Company-specific issues related to remedies (e.g., financials, sales, reliance on suppliers)	1	N/A
Serrano, Sam	Percipeint Witness Rockstar, Inc.	Live	Company-specific issues related to remedies and civil penalties	1	1
Shafer, Chad Shafer	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Shah, Nisith R	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Shutler, Brian	Percipient Witness BP West Coast Products LLC	Live	*ampm* franchise structure and relationships, and placement and posting of Proposition 65 warning signs.	1	0.5
Sides, Brian R	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25

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Joint Witness List

Name	Description	Live/Transcript	Subject of Testimony	Time (Direct)	Time (Cross)
Singcharoen, Kitikorn T	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Singh, Ashneal	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Singh, Gagneet G	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Siska, Rashanda	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Sloan, Matthew	Percipient Witness (Trader Joe's Company)	Live/Transcript	Company-specific issues related to remedies and civil penalties	1	1
Smith, Erick A	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Smith, Greg	Percipient Witness (Starbucks Corporation)	Live/Transcript	Company-specific issues related to remedies and civil penalties	1	N/A
Smith, Martyn	Plaintiff expert (testified in Phase 1)	Live	Coffee causing childhood leukemia, and mechanisms of carcinogenesis (only if defense expert depos are re-opened)	N/A	
Solario, Anthony P	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Solish, Jonathan	Defendant Expert	Live	Nature and incidents of franchise relationships.	4	1
Sotelo, Gianna M	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	
Spingarn, Neil	Plaintiff expert	Live	Analysis of acrylamide in coffee	6	3
Squires-bass, Sharon S	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	
Stachura, Ted	Percipient Witness (Equator Coffee & Teas, Inc.)	Live	Company-specific issues related to remedies and civil penalties	1	1
Stamps, Leroy	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Stewart, Jasmine	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Stookey, Jodi	Plaintiff expert	Live	Nutritional epidemiology	6	3

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Name	Description	Live/Transcript	Subject of Testimony	Time (Direct)	Time (Cross)
Storey, Paul	Person Most Knowledgeable - Rockstar, Inc.	Live	Company-specific issues related to remedies and civil penalties	1	1
Strader, Jeffrey	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	1.5	0.5
Strand, Paul	Percipient Witness (Nestle USA, Inc.)	Live	Company-specific issues related to remedies and civil penalties	1	0.5
Stratton, Letitia	Percipient Witness BP West Coast Products LLC	Live	*ampm* franchise structure and relationships, and placement and posting of Proposition 65 warning signs.	1	0.5
Sullivan, Darryl	Defendant Expert	Live	Methods used to prepare, test, and analyze samples of coffee that his laboratory tested for acrylamide concentrations in this matter, and in rebuttal to Plaintiff's experts.	4	3
Tagliaferro, Vinny	Percipient Witness (Melitta U.S.A., Inc.)	Live	Company-specific issues related to remedies and civil penalties	1	0.5
Tang, Andrew T	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Teanio, Gavino K	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Tetelboin, Vanessa K	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Teter, Jeffrey	Person Most Knowledgeable - Allegro Coffee Company	Live/Transcript	Company-specific issues related to remedies and penalties	2	N/A
Thayer, Greg	Percipient Witness (Cascade Coffee, Inc.)	Live/Transcript	Company-specific issues related to remedies and civil penalties	1	N/A
The, Tik	Percipient Witness (The Coca-Cola Company)	Live/Transcript	Company-specific issues related to remedies and civil penalties	1	N/A
Thompson, La Nita L	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Tofighi, Ali	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25

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Joint Witness List

Name	Description	Live/Transcript	Subject of Testimony	Time (Direct)	Time (Cross)
Walker, Deon A	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Walker, Sanaye N	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Wallace, Fred	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	1.5	0.5
Waraich, Gurbir	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Waring, Kristen E.	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Warrick, Ryan M.	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Washington, Derrick L.	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Weeks, Rebecca L.	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Weinberg, Carolyn	Percipient Witness (Quartermaine Coffee Roasters)	Live	Company-specific issues related to remedies and civil penalties	1	0.5
Weinstein, Roy	Defendant Expert	Live	Economic analysis of civil penalty factors.	4	1
Welsh, Doug	Percipient Witness (Peet's Coffee & Tea, LLC)	Live	Company-specific issues related to remedies and civil penalties	1	1
Wendel, Lindsey R.	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
White, Carla D.	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Wiggins, Damen T.	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Williams, Gregory G.	Percipient Witness 7-Eleven, Inc.	Live	Placement and posting of Proposition 65 warning signs.	0.5	0.25
Williams, Kyle	Percipient Witness (Godiva Chocolatier, Inc.)	Live/Transcript	Company-specific issues related to remedies and civil penalties	1	N/A

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Quantitative risk assessment and the limitations of the linearized multistage model

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1 Quantifying carcinogenic risk is an important objective for assisting in the assessment and management of risks from chemical exposure. The most widely used of the many mathematical models proposed for extrapolation of carcinogenicity data from animal studies to low dose human exposures is the linearized multistage (LMS) model. This has, in effect, become the default approach for much of Quantitative Risk Assessment (QRA). The practical properties of this model have been investigated.
2 Analysis of simulated data using the LMS model showed (i) that the Maximum Likelihood Estimate (MLE) of the low dose slope, q_1, was unstable and extremely sensitive to small changes in the data; (ii) the 95% Upper Confidence Limit (UCL) estimate, q_1*, preferred by the US Environmental Protection Agency (EPA) was insensitive with only small changes in values being obtained for large changes in the data; (iii) data sets where there was no statistical significance could give risk estimates similar to those obtained from data sets with clear dose-related effects; (iv) the size of the values of the Virtually Safe Dose (VSD) obtained did not necessarily relate to the biological interpretation of the data sets; (v) the value of q_1* obtained was closely related to the top dose used in the study.
3 Limitations of the LMS model were illustrated by examples of its use in assessing the carcinogenicity of 2, 3, 7, 8-TCDD leading to the conclusion that the existing models are not suitable for routine use in the estimation of the risk from chemical carcinogens. The use of the LMS model has been justified in part by its original derivation from a mathematical model based upon a multistage model of carcinogenesis. However, estimates of the parameters of the model used to provide estimates of low dose risk to humans have no direct relationship to specific biological event in carcinogenesis. Further developments in mathematical models and increased understanding of the biological events underlying carcinogenesis will lead to more biologically plausible QRA methods which would then justify serious consideration of QRA by regulatory authorities throughout the world.

Keywords: Quantitative Risk Assessment; carcinogens; linearized multistage model; dioxin

Introduction

Quantifying the risks associated with actions or exposures to chemicals is increasingly considered to be a desirable objective.[1] Such numerical estimates could then lead to a realistic approach to the assessment of risk, the opportunity to rank risks and to set priorities on competing actions. It could also aid in the perception and communication of risk to a wider population, such as the general public.[2] These goals have led to the development of the field of research called Quantitative Risk Assessment (QRA).

The search for realistic numerical estimates of risk is, therefore, important. The use of mathematical models to derive what are claimed to be quantitative estimates of the risk of cancer from exposure to chemicals in food, water and the environment is one area of QRA. These techniques have in most cases derived from the need for quantitative estimates of risk for regulatory purposes in the US.[3] At present, however, the UK Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment, which advises UK Government Departments on the carcinogenic risk to man from substances, does not support the routine use of QRA for chemical carcinogens.[4]

The purpose of this paper is to discuss some of the issues associated with QRA as currently practised for the assessment of risks associated with chemicals. The general thesis of the paper is that the superficially attractive approach of producing quantitative estimates is not as straight-forward as it first appears.

Reviews of the results of fitting a series of models to different data sets of rodent carcinogenicity experiments have shown: (i) many of the models can provide good fits to the observed data; (ii) they differ considerably, and predictably, in the low dose extrapolation; (iii) there are no grounds for choosing one model in preference to any other based on their statistical properties; (iv) none of the quantal models has any realistic biological basis which justifies their use; (v) the apparent similarity between the mathematical model underlying the linearized multistage (LMS) model and the biologi-

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cal concepts underlying the multistage model of carcinogenesis is superficial and does not vindicate the use of the model in QRA. The results of this review are illustrated, here, for the LMS model, the most widely used mathematical model in carcinogenicity risk assessment.

Limitations to the approaches using mathematical models for QRA to estimate the risks associated with chemical exposures are understood by those with specific expertise in the area, but have not always been appreciated by those actually carrying out risk assessments or who produce the toxicological data used in the assessments. It is the objective of this paper to illustrate some of the pitfalls associated with the existing methods and indicate ways that QRA can develop positively. The problems with the LMS model will be illustrated using the type of data sets familiar to the practising toxicologist rather than being illustrated using a theoretical mathematical approach.

Problems with definitions

The scientific discipline concerned with the analysis, estimation and assessment of risk suffers from considerable confusion because of the inconsistencies of the definitions used by different organisations. In this paper the terminology will be broadly based upon that developed by the US National Academy of Sciences/National Research Council (NAS/NRC).[5] This is not because their terminology is inherently better but because it is more closely applied to the topics involved in QRA, which, in general, has had much greater use in the USA than elsewhere. The usual distinction between hazard and risk will be used, with *hazard* being an inherent property of a substance or event and *risk* being the probability that such an event will occur.[6,7]

The US distinction between risk assessment and risk management (Figure 1) will be adhered to : risk assessment is a scientific attempt to identify and estimate the true risks while risk management is where a choice is made from the various options that have been identified for regulatory actions. In the context of the US regulatory system the areas are distinct, with information being passed from the scientific assessor to the risk manager through the equivalent of a 'Chinese Wall', which has the objective of delineating the scientific aspect, as an objective value-free statement, from the risk management options, which involve a mixture of economic, societal and political factors.

Risk assessment in this context is then split into four stages: the qualitative stage of hazard identification, dose-response modelling, the assessment of exposures, and finally, a risk characterization stage where all the scientific evidence is consolidated into a package that can be handed over to the risk manager. Although there are elements to this approach in the UK procedures, there are also some differences and the UK approach is less prescriptive.[8]

Even the definitions of the terms risk assessment and QRA can vary depending upon the practitioner. Both terms are used by some to refer to anything to do with the analysis of risk where probabilities are involved. Others restrict their use to what the NAS/NRC call 'Risk assessment'. Some limit QRA solely to the dose-response modelling stage using the term synonymously with 'Mathematical modelling'. In this paper QRA will be considered to be the application of mathematical approaches to derive estimates of risk to the human population. Most attention, though, will be concentrated on the use of mathematical modelling of dose-response relationships in QRA, but other aspects of numerical methods in risk assessment will also be touched on. These mathematical models aim to provide a method for estimating the effects of exposures at low doses from the results of experiments on animals or exposure of humans at higher doses.

The uses of QRA

A persuasive argument was made for the use of QRA by Anderson and colleagues in the Carcinogen

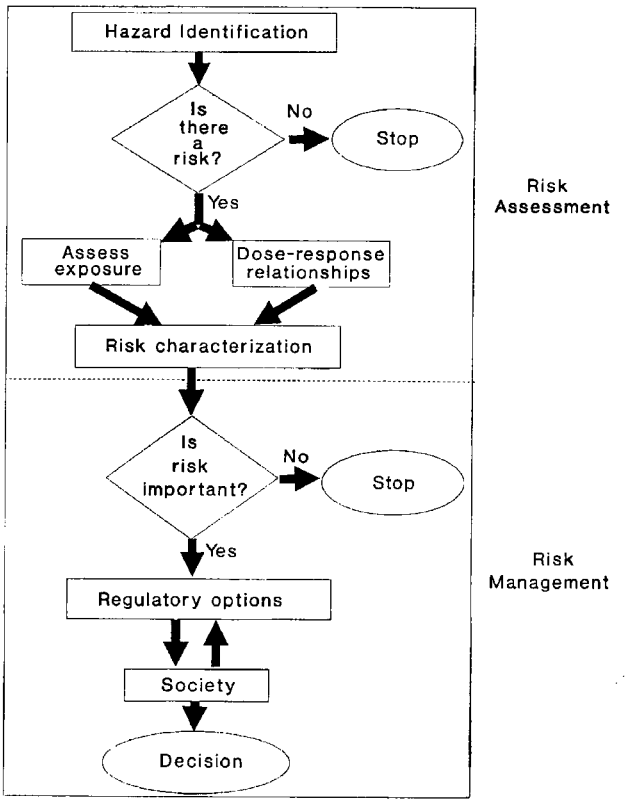


Figure 1 Diagrammatic representation of the US risk assessment/risk management process illustrating the division between risk assessment and risk management and the four components of the risk assessment process: hazard identification, dose-response relationship, exposure assessment and risk characterization.

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Assessment Group of the US Environmental Protection Agency (EPA).[9,10] Anderson *et al* identified a number of circumstances where QRA might help in the analysis and management of risks. Examples were given of how chemicals such as suspected carcinogenic air pollutants could be ranked for setting priorities; how the risks remaining after regulating a chemical could be compared with those before and those from other unregulated chemicals; how estimates of risk could be incorporated into a risk-benefit analysis; and how the concentrations of carcinogens in drinking water associated with a specific small level of risk, such as a 10^{-5} lifetime risk of cancer, could be set as targets below which concentrations should be reduced.

Anderson *et al* illustrated the use of risk estimates derived from mathematical models applied, in most cases, to data from the long-term rodent cancer bioassay (LTRCB). One example was the ranking of a range of potential carcinogenic air pollutants based upon their carcinogenic potency from the LTRCB, where the potency is measured by the lifetime cancer risk resulting from exposure to 1 $\mu g/m^3$ in air for a lifetime. Anderson *et al*'s listing shows a very high risk from 2, 3, 7, 8-TCDD and lower risks from the known human carcinogens, vinyl chloride and benzene, when expressed on a common $\mu g/m^3$ scale.

A series of mathematical models were developed in the 1970s and 1980s to carry out low-dose extrapolation from the tumour incidences found in the LTRCB; these included the probit, logit, Weibull, one- and multi-hit and the multistage models. The properties of these models were well-known, including their general ability to fit the observed data, but providing widely differing estimates of risks at low doses, and a predictable ranking of low dose risks from the data sets.[11] Although the US Food and Drug Administration (FDA) had begun QRA approaches, based upon a modified Mantel-Bryan approach,[12,13] it was the US EPA in the 1980s that developed standardised approaches, first using a one-hit model and then a multistage model.[9] The EPA Carcinogen Risk Assessment Guidelines of 1986, in effect, specified one variant of the multistage model, the LMS, as its default model.[14]

The linearized multistage model

The 1986 EPA Guidelines specified that '(I)n the absence of adequate information to the contrary, the linearized multistage procedure will be employed' and that '(C)onsiderable uncertainty will remain concerning responses at low doses; therefore in

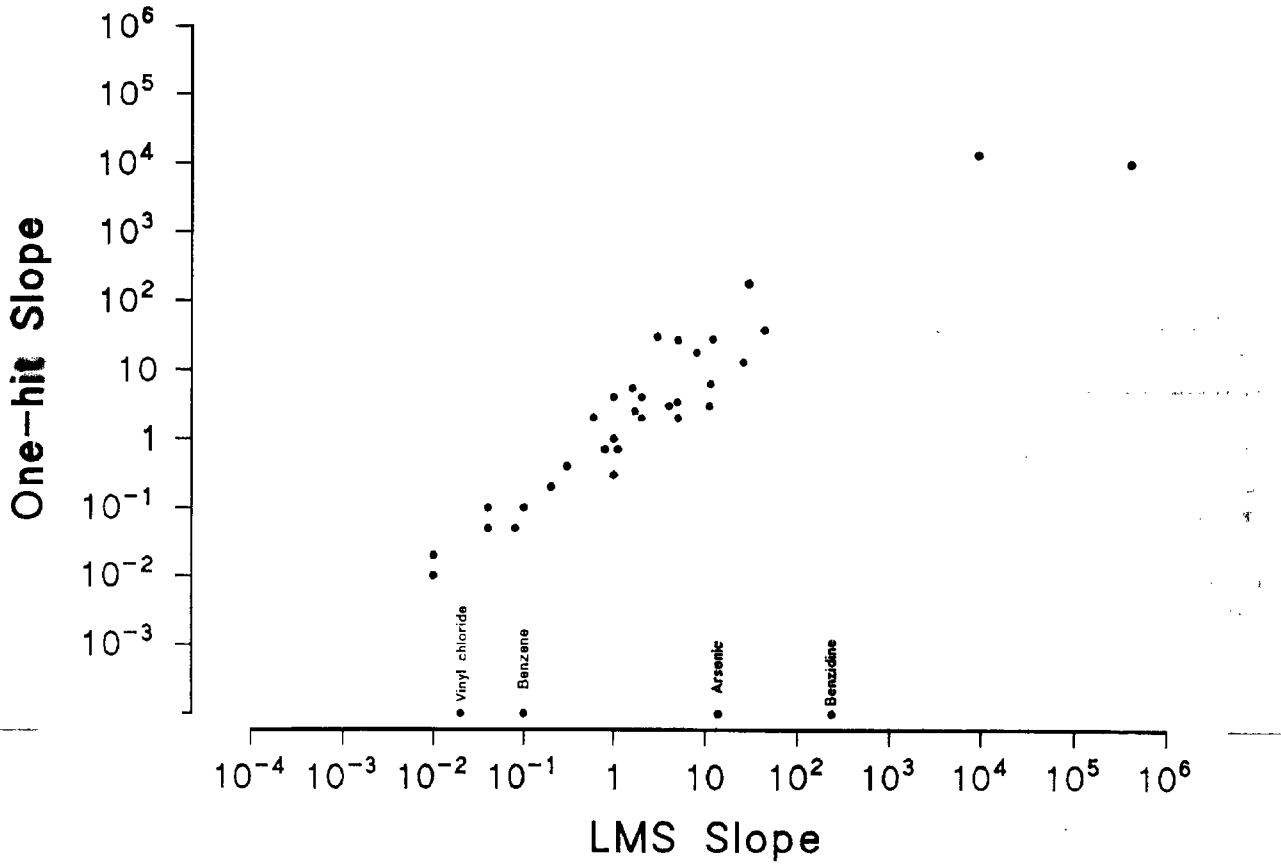


Figure 2 A plot of the one-hit model and LMS model slopes, listed by Anderson (1988) (Reference 10) illustrating the similarity of the two values. In four cases: benzene, benzidine, vinyl chloride and arsenic the LMS estimates were derived from epidemiological data and a one-hit slope was not given.

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most cases an upper-bound risk estimate using the linearized multistage model should be presented'.[14]

The linearised multistage model used by the EPA developed from the multistage model of cancer developed by Armitage and Doll[15] to explain epidemiological data on human cancers. The model was reformulated by Crump and co-workers[16,17] to provide a convenient model for use within the US regulatory framework.[14] A detailed explanation of how the EPA has used the model is given by Anderson *et al.*[9] Although the 1986 EPA Guidelines stress that other models could be considered, the LMS can be considered to be the 'default' model,[18] as it is used in the absence of information suggesting the use of a different model.

The original Armitage-Doll multistage mathematical model assumed that the carcinogenic mechanism could be considered as a series of somatic mutations. After a cell has gone through these series of mutational stages it became malignant and proceeded to develop into a tumour. It was assumed that several random hits or biological events were required in a specific sequence before a tumour developed. The model assumed, mathematically, that a carcinogen would affect at least one of the transitions between the different mutational stages.

The multistage model was chosen for regulatory purposes, because such a mathematical model appeared to have parallels with biological explanations of cancer as a cell passing through a series of stages as initiation, promotion and progression. The US Congress' Office of Technology Assessment (OTA)[18] reported that this apparent compatibility between the mathematics and the biology was one factor favouring its use. Anderson *et al*[9,10] provide a fuller discussion of the reasons for the choice of the LMS, and, while noting differences between these two types of model, stressed the 'biological feasibility of the LMS model'.

The original Armitage-Doll model was modified by making the assumption that the rates of occurrence of the different changes were all directly proportional to the dose of a carcinogen. This allowed the cumulative tumour incidence to be approximated by a relatively simple equation. This equation could then be further modified to take into account a background incidence of the changes in the absence of any dose of the chemical (d=0). Some of the terms in the formulation could then be related to the spontaneous occurrence at each stage, and others to the dose-response relationship relating to each stage.

An alternative formulation of the multistage model as a polynomial with respect to dose was developed by Crump (Figure 3). This formulation assumed that all carcinogenesis operated by a common mechanism, and any carcinogen increased that part of the ongoing process. This formulation has been included in a number of software packages. It makes the assumption that all the q_i values are non-negative. The relationship is essentially linear at low doses. This model assumes that any 'dosage effect' has the same mechanism as that which causes the background incidence. Low-dose linearity follows directly from this additive assumption, provided that any fraction of the background effect is additive no matter how small.

A 'best fit' curve is fitted to the data obtained from the LTRCB using computer programs, such as GLOBAL86, Tox-Risk (Clement International Corporation, Ruston, Louisiana), or MSTAGE (Crouch, personal communication). The estimates of the parameters, q_0, q_1...q_i obtained are called Maximum Likelihood Estimates (MLE), based upon the statistical procedure used for fitting the curve, and can be considered as 'best fit' estimates. Provided the fit of the model is satisfactory, the estimates of these parameters are used to extrapolate (technically, as there is a control group, this should be 'interpolate') to low dose exposures (as illustrated by considering Figure 4 to be part of the box in Figure 3). Anderson *et al*[9] used a X^2 fit with a P value greater than 0.01 as the criterion for suitability of fit; if the fit is poorer, then the top dose data are excluded and further rounds of model fitting carried out until an acceptable fit is obtained.

Some of the assumptions implicit in the LMS version of the multistage model used for regulatory purposes can clearly no longer be considered biologically realistic. These assumptions include acceptance that the order of the progression of the cell through the stages is fixed and irreversible; that the 'waiting times' in the various stages are statistically independent and follow the exponential distribution when the exposure is constant, and

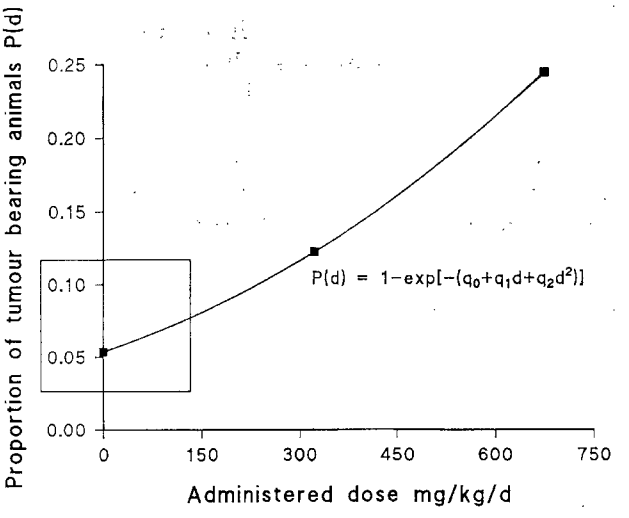


Figure 3 A diagrammatic representation of the fit of the multistage model to data. Low dose extrapolation as shown in Figure 4 takes place in the box shown in the diagram.

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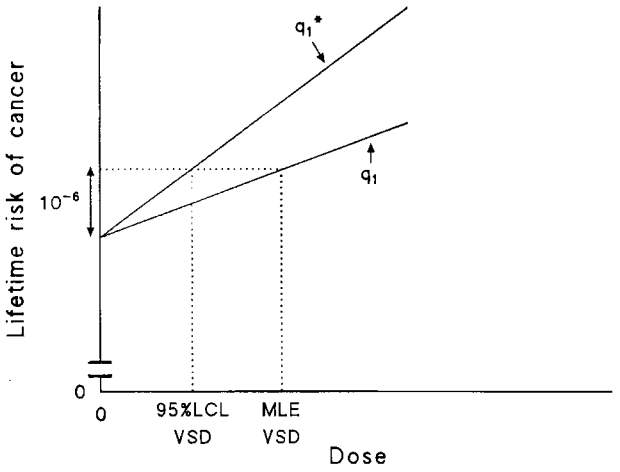


Figure 4 A diagram to illustrate the use of the LMS model to estimate MLE and LCL estimates of the VSD for an extra risk of 10^{-6}. The diagram shows the MLE of the low dose slope, q_1, and the 95% UCL of the low dose slope, q_1* as continuous lines. The dotted lines show the derivation of estimates of dose which would result in a one in a million increased lifetime cancer risk based on the model. The use of the MLE slope, q_1, leads to the MLE of the VSD while use of the upper bound UCL slope, q_1*, leads to the LCL estimate of the VSD.

that cells go through this progression independently of one another, so that the effect of cell division is missed.

In the biological version of the multistage model a colony of cells can be considered as progressing through stages on the way to cancer. However, in the statistical version of the multistage model, the individual cell executes the equivalent of a Markov chain through a fixed order of states along the way to cancer, with the transition rates being linear functions of dose.

It is important to realise that although the LMS model has some degree of biological underpinning, there is no specific biological interpretation of any of the parameters estimated by the LMS model, or direct correspondence with measures of the underlying biological events, such as cell mutation, differentiation or death rates. Instead, the estimate of q_0 is related to the underlying spontaneous or control incidence of tumours, while the other q_is, particularly estimates of q_1, could be interpreted as measures of carcinogenic potency at low doses. The parameters should, therefore, be considered solely as mathematical values, which provide a good fit between the formulation of the model and the data from the LTRCB.

It is important, however, in any criticism of the limitations of the LMS model used specifically for regulatory purposes that these criticisms do not detract from the considerable potential that multistage models in general have to provide a credible approach to the investigation of problems in carcinogenesis. In this sense the approach of Moolgavkar and co-workers,[19] which builds upon the original Armitage-Doll model, can provide a helpful tool for investigating biological phenomena, even though it may not be directly relevant or appropriate to solving a regulatory problem.

The LMS model, in fact, superseded the one-hit model long used in radiation work and originally favoured by the EPA, because the LMS model provided better fits to data. (The change in regulatory favour occurred in the late 1970s, when the EPA was developing Water Quality Criteria to meet its responsibilities under the US Safe Drinking Water Act, using the one-hit model for its draft in 1979 and the LMS model for the final report in 1980). In practice, however, the estimates of low dose risk obtained from the LMS model are very similar to those obtained using the one-hit model (Figure 2).

The linear component of the LMS model, q_1, is approximately equivalent to the slope at low doses of the dose-response relationship between the tumour incidence P(d) and the dose (d):

$$P(d) \approx q_1 d \text{ where } q_1 \text{ is the MLE}$$

This linearity at low dose is a property of the formulation developed for the multistage model and is considered by proponents to be one of its important properties. This linear component of the polynomial, q_1, is used to carry out low dose extrapolation. The linear response at low doses is considered to be conservative with regard to risk, as the dose-response relationship at low doses may well be sub-linear. Although supra-linearity at low doses cannot be excluded, it is usually considered to be unlikely.

The 95% confidence limits of the estimate of q_1 can also be calculated. The 95% upper confidence limit (95%UCL) is termed q_1* and is central to the EPA's use of the LMS model in QRA. q_1* represents an upper bound or 'worst case' estimate of the dose-response relationship at low doses. It is considered a 'plausible upper bound', because it is unlikely that the true dose-response relationship will have a slope higher than q_1*, and it is probably considerably lower and may even be zero (as would be the case if there was a threshold). Use of the 95%UCL as the 'default', therefore, may have considerable conservatism incorporated into it.

The estimates of the parameters, q_1 and q_1* are used to provide estimates either of the risks associated with specific doses, or conversely the dose associated with a specific increase in risk. Figure 4 shows diagrammatically how the risk associated with a 1 in a million ($1/10^6$) extra lifetime incidence of cancer in the experimental species can be related to the dose. (This dose is often referred to as the virtually safe dose or VSD). Using the 'best fit' MLE, q_1, a MLE of the virtually safe dose is obtained by extrapolation; using the steeper 95% UCL of q_1, q_1*, extrapolation results in a 95% *lower* confidence

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limit for the VSD (95%LCL of the VSD). Use of the UCL for q_1* and the LCL for the VSD can be a source of confusion.

Increasingly organisations such as the EPA use the term Reference Specific Dose (RsD) to refer to the 95% LCL of the VSD defined above. They prefer this terminology because it does not carry the connotations that the word 'safety' can imply in an area where absolute safety and zero risk are not considered achievable.

An illustration of the use of the LMS

The only data used in fitting the LMS model are the dose levels and the numbers of animals bearing the tumour under study, and the numbers examined in each dose group. In the case of a standard control and three dose level LTRCB this is just twelve items of data.

A worked example of the LMS model is provided by the data of Leung and Paustenbach[20] for hepatic tumours of rats exposed to three different oral dose levels of 1,3-dioxane. The data are the dose levels, the number of animals exposed and the number of animals identified with tumours. The LMS model does not use information on the animal's lifespan or whether any tumours identified have a context of observation, i.e. whether they are considered fatal or incidental.[21]

A computer program can be used to fit the multistage model and obtain estimates of the parameters (Figure 5). In this case MLEs of 0.00929 and 1.15×10^{-10} are obtained for q_0 and q_3; the MLEs for q_1 and q_2 are set to zero. (The formulation of the LMS model constrains the values of q_i to be greater than or equal to 0; negative values are not allowed). The 95%UCL of q_1, q_1* is estimated as 1.81×10^{-4}. The VSD associated with an increased lifetime cancer risk of 10^{-6} is obtained by dividing 10^{-6} by q_1 and q_1*. This produces the MLE and 95%LCL estimates of the VSD of infinity and 0.0055 mg/kg/day respectively. The use of the LMS model in this case suggests that the best estimate of risk at low dose is zero, or that there is no dose of the chemical which increases the risk by 10^{-6}. (In practice, software such as Tox-Risk which includes a low-dose extrapolation stage in the package, provides a VSD, which is derived using the other parameters in the low dose estimation. Here the MLE slope is estimated as 4.9×10^{-8} $(mg/kg/day)^{-1}$ and the MLE VSD as 20.5 mg/kg/day by Tox-Risk).

The failure of the LMS model to provide a non-zero estimate of q_1 for some data sets especially those with high dose effects, was one reason that the EPA chose to use the UCL, q_1*, rather than the MLE of q_1.[18]

The values of q_1* have been considered as estimates of carcinogenic potency and have been called the unit carcinogenic risk or the Carcinogen Potency Factor (CPF). It is these estimates which have now been tabulated by a number of organisations (see, for instance, the table of 'slopes' of carcinogenic potencies presented by the US OTA[18])

1) Experimental results (number of rats with hepatic tumours/number of rats exposed)

	Oral dose levels mg/kg/d			
	0	14.3	121	1184
Hepatic tumours	2/106	0/110	1/106	12/66

2) Application of Linearized Multistage (LMS) Model

$$P(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + q_3 d^3)]$$

3) Estimation of MLE parameters of LMS model

	MLE
q_0	$= 9.29 \times 10^{-3}$
q_1	$= 0$
q_2	$= 0$
q_3	$= 1.15 \times 10^{-10}$

4) Estimation of 95% confidence limits of q_i

q_1^*, the 95% Upper confidence limit (UCL) for q_1, is 1.81×10^{-4}

The 95% Lower confidence limit (LCL) for q_1 is 0

5) Estimation of VSD

$$VSD\ (95\%LCL) = 10^{-6} / q_1^*$$
$$= 10^{-6} / 1.81 \times 10^{-4}$$
$$= 0.0055\ mg/kg/day$$

Figure 5 Application of LMS model to data on hepatic tumours in rats in a study of rats dosed orally with 1,3-dioxane (data taken from Leung & Paustenbach (1990) (Reference 20).

The use of the q_1 values*

Figure 6 shows a flowchart of how values of q_1* are used by organisations such as the EPA to provide quantitative estimates of risk to the human population. In the hazard identification stage a decision is made on whether or not to classify the chemical as a rodent carcinogen. Data from the LTRCB are used as described above to provide estimates of the low dose carcinogenic potency from estimates of q_1*. These estimates are then modified by the application of a scaling factor to incorporate differences between species. This factor tries to relate exposure in the experimental species, usually a rodent, to that in the target species, usually the human population.

The factor may be based on a direct mg/kg/day basis or may reflect species differences in surface area or metabolic rate. Until recently the FDA used a direct body weight conversion, while the EPA used the ratio of body surface areas for their species conversion factors. The body surface area approach was equivalent to a body weight exponent of 0.67; the effect was that estimates of the VSD obtained

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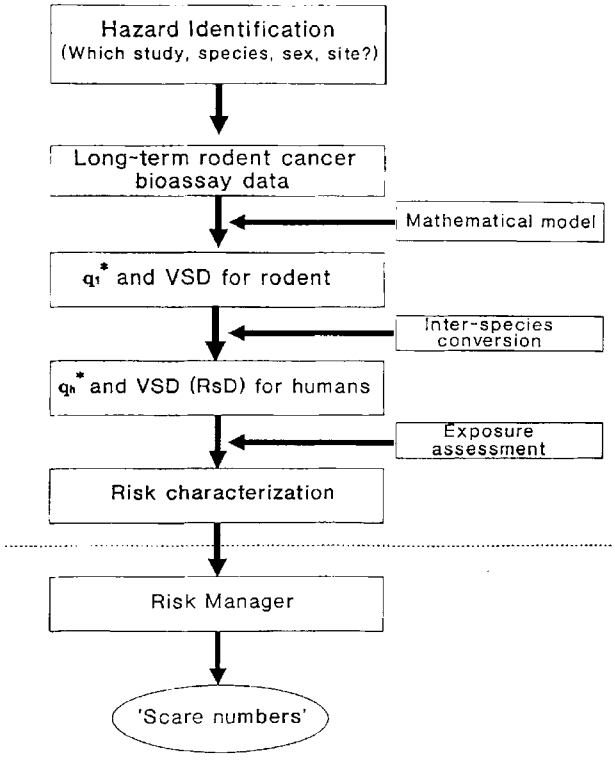


Figure 6 Flow chart of the stages in the development of quantitative estimates of risk to the human population. Diagram shows the development of numerical estimates of risk based upon data from LTRCBs, followed by inter-species conversion and assessment of environmental exposure. The results of the risk assessment are characterized and handed over for risk management. Misunderstanding over the derivation and the degrees of conservatism in the estimates can lead to such quantitative estimates of risk generating concern (referred to here as 'Scare numbers').

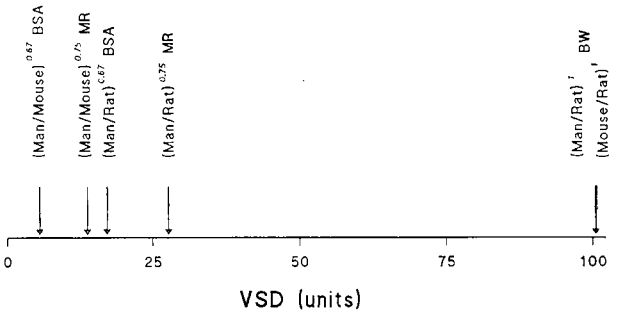


Figure 7 VSDs using different inter-species scaling factors relative to the use of scaling based upon body weight. BW refers to inter-species scaling based on body weight; BSA to scaling based on body surface area and MR to scaling based on metabolic rate.

using the surface area conversion factor would be lower than those using a ratio of body weights for the same data (Figure 7). The differences in approach between the various US regulatory agenices in their choice of scaling factor has led to an attempt to use a factor based upon metabolic rate, which has a body weight exponent of 0.75. (The scientific argument behind the choice of 0.75 is reviewed by Sidhu[22]). This has now been agreed as a common scaling factor by the EPA and FDA.[23] The implication is that VSDs obtained using this compromise are smaller than those using the body weight approach, and slightly larger than those using the surface area conversion factor.

The human VSD is then compared with likely environmental exposures. The choice of scenarios for individual exposure can have a considerable effect on the final estimates of risk to the human population in terms of the number of people likely to be affected. The choice of whether the maximum permitted levels or average levels are used; the average or the potentially most susceptible individual should be considered; the exposure is considered continuously at the maximum concentration, or more realistic intermittent exposures should be used have to be considered. In some cases estimates of risk are based upon the Maximum Exposed Individual (MEI), derived by considering the 'worst possible case' of a susceptible individual being exposed to the maximum possible exposures from all possible routes for the whole of the lifetime of that person. The choice of how to assess exposures and to incorporate the variability in exposure is crucial to the final assessment of risk. (This aspect of the risk assessment process varies considerably from case to case and will not be discussed further here). The data derived from the LTRCB and the exposure assessment are then integrated into a package in the risk characterisation phase of the assessment and are then passed, in the NAS/NRC framework, to the Risk Manager.

There is a debate over how much information should be provided by the Risk Assessor to the Risk Manager. Some argue that a detailed description of the risk assessment, the assumptions underlying it and the equivalent of a sensitivity analysis of the conclusions should be provided to ensure a complete appreciation of the findings, whilst others press for a more restricted set of results, such as the EPA's 'boilerplate' approach to its risk summaries.[18] Proponents of providing more information argue that all restricted approaches result in over-simplification, leading to misunderstanding and subsequent problems in risk perception and communication to a wider public.

Examples of the LMS model in practice

A fuller worked example of the implications of the LMS model and the QRA approach, in general, will be illustrated by risk assessments carried out on 2, 3, 7, 8-TCDD (dioxin). 2, 3, 7, 8-TCDD has been chosen because it represents a model compound for risk assessment. Considerable differences exist in the guidance levels produced by different regulatory bodies,[24] as illustrated in Figure 8. US regulatory agencies using mathematical models have set conservative VSDs (RsD), while Canadian, European and some US state agencies and the

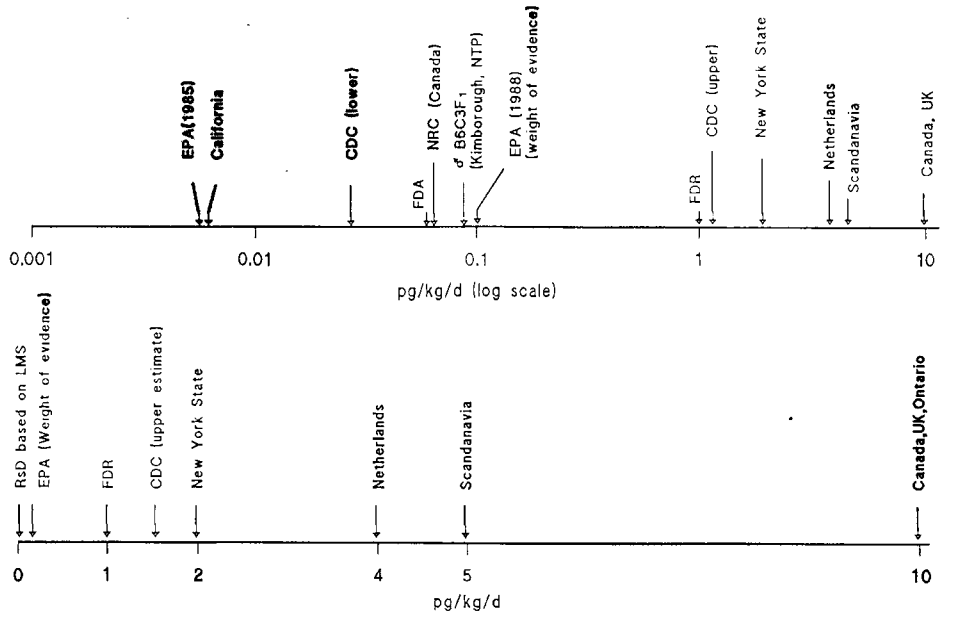


Figure 8 Diagrammatic representation of the guidance levels set by different regulatory agencies for 2, 3, 7, 8-TCDD.

World Health Organisation (WHO) have set Tolerable Daily Intakes (TDIs) or guidance levels, which are orders of magnitude higher, using more traditional No-Observed Adverse Effect Level/Safety Factor (NOAEL/SF) approaches.[25] The widest extreme is between the value of 6.4 fg/kg/day set by the EPA and the 10 pg/kg/day level derived by a number of other agencies.

The differences in the approaches can be clearly seen in the lower part of Figure 8, where the concentration of TCDD is on a linear rather than a logarithmic scale. The mathematical modelling approaches are concentrated to the far left of the scale.

Part of this difference derives from whether or not a chemical is determined to be a carcinogen in the hazard identification stage, and if so whether it is considered a genotoxic or non-genotoxic chemical. Those agencies which differentiate between genotoxic and non-genotoxic carcinogens for regulatory purposes are prepared to accept the existence of a threshold for non-genotoxic carcinogens, and they derive guidance levels using a traditional safety factor approach. The EPA's 1986 guidelines drew no distinction based on mechanism and considered all substances positive in bioassays to be complete carcinogens 'unless there is evidence to the contrary'.[14] The EPA is currently both reviewing its carcinogen risk assessment guidelines[26] and carrying out a new review of the health effects of 2, 3, 7, 8-TCDD.[27–29] The US EPA has also produced in July 1994 'Draft Revisions to Guidelines for Carcinogen Risk Assessment. A Review Draft'.

The use of QRA for 2, 3, 7, 8-TCDD has been a continual source of controversy. An attempt was made by the EPA to revise its original VSD of 6.4 fg/kg/day to 100 fg/kg/day based upon a weight of evidence approach.[30] Although a draft proposing this level was produced, it was subsequently withdrawn and the EPA's value of 6.4 fg/kg/day remains in place and can still be found in the IRIS database and the ATSDR listings. It was thought that a more mechanistic model involving the interaction of 2, 3, 7, 8-TCDD and the Ah receptor would be developed to provide a threshold model. However, EPA officials have lowered their expectations of this possibility and are stressing the apparent linearity at low doses of the results produced by Lucier and co-workers.[31,32] These results are interpreted as showing linearity of the response to 2, 3, 7, 8-TCDD with the Ah receptor down to the lowest dose. This low dose was, however, 100 pg/kg/day – still an order of magnitude above the highest guidance level in Figure 8.

It is instructive to see how different agencies have applied QRA approaches to the LTRCB data to obtain RsDs or guidance levels. Three examples will be given: the approach of the US EPA, the US FDA and the UK Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (COT).

All three agencies used data on tumour incidence from the same long-term bioassay of 2, 3, 7, 8-TCDD: the Kociba *et al* Sprague Dawley rat study.[33] Two pathologists reviewed the material from the female rats, reporting different numbers of tumours in the dose groups. Subsequently the material was read by a further group of pathologists, the Pathology Working Group (PWG), who proposed a different set of diagnoses.

The original data were fitted by the EPA using the LMS model to produce values of q_1* (Table 1). The values of q_1* for the data from the two pathologists were very similar, despite large differences in the

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Table 1 Derivation of RsD for 2,3,7,8-TCDD by the US EPA using the Kociba *et al* (1978) female rat data

Pathologist		*'A'*			*'B'*			
Dose (μg/kg/day)	*0*	*0.001*	*0.01*	*0.1*	*0*	*0.001*	*0.01*	*0.1*
Tumour incidence	*9/85*	*3/48*	*18/48*	*34/40*	*16/85*	*8/48*	*27/48*	*34/40*
Linearized multistage model								
q_1^* =		2.82×10^4 (mg/kg/day)$^{-1}$			3.00×10^4 (mg/kg/day)$^{-1}$			
Correction Factor=		dose/surface area		$\left(\frac{70}{0.45}\right)^{1/3}$				
q_1^* =		1.51×10^5 (mg/kg/day)$^{-1}$			1.61×10^5 (mg/kg/day)$^{-1}$			
q_1^* =				1.56×10^5 (mg/kg/day)$^{-1}$ (geometric mean of two estimates)				
RsD =				$\frac{1 \times 10^{-6}}{1.56 \times 10^5}$				
=				6.43 fg/kg/day				

The Kociba *et al.* (1978) 2-year study with oral administration was used to derive the RsD. Female Sprague Dawley rats were considered the most sensitive sex and species. Tumour data were pooled sites (liver, lung, hard palate/nasal turbinates). Animals that died during the first year of the study were not included in the analyses. Two different pathologists ('A' and 'B') provided diagnoses.

number of animals with tumours diagnosed in the control and low dose groups, suggesting that estimates of q_1^* were more affected by results at high doses than effects at low doses. The estimates of q_1^* were then combined by taking the geometric mean of the two values and this was multiplied by a scaling factor based upon surface area (species correction factor) of 5.4. This was based upon a 450 g rat and a 70 kg human to obtain a q_h^* (a q_1^* value for humans) of 1.56×10^5 (mg/kg/day)$^{-1}$ (This is identical to the slope value in Table 3.24 of the 1988 OTA report[18].) This divided into 10^{-6} gives the VSD of 6.4 fg/kg/day, which has been widely quoted and is the value shown in Figure 8.

The Kociba *et al*[33] study had been identified by the EPA as the most appropriate study for risk assessment; the female rat was considered the most sensitive sex and species, and the LMS model was applied to all tumour sites; the data included in the LMS model consisted of combined liver, lung, hard palate and nasal turbinate tumours.

The same study was used by the US FDA to obtain their VSD of 57.2 fg/kg/day.[30] The FDA also used the female rat data but only liver tumours were analysed.[34] However, this was the major tumour site, and the number of liver tumours in the FDA's analysis were, in fact, identical in number to all the tumours identified by one of the pathologists. The denominators in the FDA data were higher. This was because animals which died in the first year of the study before any tumours were found were excluded from the EPA's analysis. The FDA used, in fact, an alternative low dose extrapolation method, the Gaylor-Kodell linear interpolation procedure;[35]

Table 2 Values of RsD and TDI/Guidance values obtained using QRA or Safety Factor approach by different regulatory authorities based upon different interpretations of the Kociba *et al* study

(a) Risk Specific Dose (RsD) for dioxin using mathematical models

	RsD fg/kg/day	
EPA (1985)	**6.4**	(LMS)
EPA (1988) (Weight of evidence)	**100**	(LMS)
FDA (1983)	57.2	(linear interpolation)
FDA (1991)	120.0	(linear interpolation)
CDC (1984)	28.0	(lower estimate)(LMS)
	1400	(upper estimate)
NRC (Canada)	65	(LMS)
California	6.7	(LMS)

(b) TDI/Guidance values for dioxin using Safety Factor approach

	TDI fg/kg/day	*SF*	*NOAEL μg/kg/day*
Germany	1000–10000	100–1000	0.001
New York State	2000	500	0.001
Netherlands	4000	250	0.001
Health & Welfare Canada & Ontario	10000	100	0.001
Nordic/Denmark	5000	200	0.001
Switzerland	10000	100	0.001
UK	10000 (nodules)	100	0.001
	10000 (carcinomas)	1000	0.01

Table 3 Sensitivity analysis of results of LMS model in QRAs carried out by the FDA and EPA for 2,3,7,8-TCDD. FDA and EPA pathology of 2,3,7,8-TCDD data

	Doses (μg/kg/day)					
	0	*0.001*	*0.01*	*0.1*	q_1	q_1*
FDA						
	9/86	3/50	18/50	34/48	1.29	1.75
EPA ('A')						
	9/85	3/48	18/48	34/40	2.08	2.82
EPA ('B')						
	16/85	8/48	27/48	34/40	2.12	2.99
(1) Reducing FDA top dose denominator by 8						
	9/86	3/50	18/50	34/40	2.06	2.78
(2) Increasing FDA intermediate numerators by 1						
	9/86	4/50	19/50	34/48	1.29	1.76
(3) Increasing FDA top dose numerator by 1						
	9/86	3/50	18/50	35/48	1.38	1.85
(4) Decreasing FDA top dose denominator by 1						
	9/86	3/50	18/50	34/47	1.36	1.83

The table shows the number of rats with tumours out of the total number examined in each dose group based upon the diagnoses used by the US EPA and FDA together with the effect of a sensitivity analysis where the numbers of animals with tumours or examined are changed. q_1 is the MLE estimate of the lifetime risk of cancer per μg/kg/day q_1* is the 95% UCL estimate of the lifetime risk of cancer per μg/kg/day.

however, this method gives similar results to those of the LMS model. The estimate of q_1* from the FDA data set is about half as steep as that from the EPA's data set, and they used a body weight conversion which was equivalent to a scaling factor of 1. As a consequence, the estimate of q_h* is about an order of magnitude lower and the VSD an order higher.

A sensitivity analysis of the data by us shows how reducing the denominator of the top dose group in the FDA data by 8 produces q_1* values similar to that of the EPA data sets (Table 3). Increasing the intermediate dose numerators by 1 only changed the FDA's q_1* values slightly, but increasing the numerator of the top dose group by 1 had a larger effect on q_1*. In this data set, effects at the top dose of the study produced larger effects on the extrapolated low doses than changes to values at the lowest observed doses.

The UK COT in its review of 2, 3, 7, 8-TCDD considered that a safety factor approach was appropriate after the UK's Committee on Mutagenicity had concluded that it was unlikely that the carcinogenicity of TCDD was due to a mutagenic mechanism.[36] It also used the revised diagnosis of the tumours carried out by the PWG, which divided the tumours into two types: hepatocellular adenomas or nodules and hepatocellular carcinomas. Using this division they derived a NOAEL for hepatocellular nodules of 0.001 μg/kg/day and 0.01 μg/kg/day for the carcinomas. They then applied a safety factor of 100 for the non-carcinogenic endpoint (the nodules) and 1000 for the carcinogenic endpoint (the carcinomas) to arrive, in both cases, at a guidance level of 10 pg/kg/day. Most other authorities that used a NOAEL approach derived a NOAEL of 0.01 μg/kg/day from these data and applied a safety factor of between 100 and 1000.

The PWG's diagnoses of the Kociba *et al* data have been used to conduct further estimates of risk using both the hepatocellular carcinoma and the nodule data. Mathematical models, which made use of more information, such as the time-to-tumour data, and the biologically based Moolgavkar-Venzon-Knudson (MVK) model, were used. Although these different approaches are less conservative they would still be located on the far left side of Figure 8b.[30]

This example of the use of the LMS model for QRA shows how few of the biological data are actually used in the derivation of an estimate of risk. It illustrates the subjective and possibly arbitrary elements in the choice of data to include or exclude from the estimation. It also shows that at stages such as the choice of estimate to use, the choice of scaling factor and the choice of data set, the more conservative option is chosen in each case. The next section will illustrate some of the limitations associated with the LMS model itself.

Limitations of the LMS

Data sets were created to illustrate specific features of the estimates of q_1 and q_1* and thereby to, provide the non-mathematically orientated toxicologist with practical examples of the consequences of using the LMS model on data representative of those produced by 'real-life' LTRCB. Data were analysed using the MSTAGE and Tox-Risk computer programs.

(1) q_1 is unstable and can be zero.

The EPA chose q_1*, the UCL estimate, rather than the MLE, q_1, in part because it provided a highly conservative estimate of risk, and also because the MLE value, q_1, could be highly variable.[18] The formulation of the value of the LMS model constrains estimates of the parameters, q_i to be either zero on non-negative. Under many circumstances this results in the 'best estimate' of the linear component of the polynomial being set to zero. Those cases are where there is a steep curvi-linear response, with a high proportion of tumour-bearing animals at the highest dose. The estimate of q_1 will also be set to zero in the case where there is no dose-response relationship.

The change, however, from q_1 being set to zero and it having a non-zero value is abrupt and can depend upon the identification of one more or one less tumour. Table 4 illustrates a number of cases where a single tumour alters the value of q_1. The value of q_1 is also not necessarily correlated with the value of q_1* obtained from the same dataset. This is illustrated in Figure 9, where the results are shown of generating a set of 50 simulated LTRCB data sets

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Table 4 Example of data sets resulting in unstable values of q_1 and showing values of q_1 are very sensitive to small changes in the tumour incidence

Dose levels				
Control	*Low*	*Medium*	*High*	
0	*10*	*100*	*1000*	q_1
0	0	0	10	0
0	**0**	**1**	**10**	1.77×10^{-4}
1	**1**	**4**	**50**	0
0	1	4	50	8.52×10^{-4}
45	46	44	46	0
44	45	46	46	2.64×10^{-4}
0	**1**	**0**	**2**	0
0	**0**	**1**	**2**	5.09×10^{-5}
0	**0**	**0**	**5**	**0**
0	0	1	5	1.13×10^{-4}

q_1 is the MLE estimate of the lifetime risk of cancer per unit dose. Table shows hypothetical sets of cancer bioassay data where numbers represent number of animals with a tumour in group sizes of 50 at each dose level. Dose levels for four groups (control, low, medium and high) are arbitrary units which could, for instance, represent mg/kg/day or ppm.

using the random number generating facility of the statistical package Minitab. The assumption was made that there were no treatment-related effects and the control and all the treated groups had the same underlying background incidence. Experiments with a negative control and 3 log-spaced doses, with a sample size of 50 animals per dose level, and the same background/spontaneous incidence of 10% were simulated. Estimates of q_1 and q_1* were obtained using MSTAGE. (Similar results were obtained using Tox-Risk). Figure 9 shows that q_1* can take a wide range of values for those cases in this data set where q_1 was set to zero. In only a small proportion of the experiments, where a slight dose-response relationship appeared by chance in the data, were the two estimates correlated. The two sets of data with the most extreme values of q_1* differed considerably in their estimates of q_1: (the data set 5, 4, 4, 11 had q_1=0 while 3, 2, 5, 11 had $q_1 = 2 \times 10^{-4}$).

The value of q_1 changed abruptly from a value of about 2×10^{-4} to zero, except that in a small number of cases a very small non-negative value of q_1 was given; an example is the data set 4, 2, 7, 4 with a q_1 value of 8.42×10^{-8}. These very small non-zero values of q_1 seem to be associated with a specific S-shaped dose-response relationship.

These data confirm that q_1 is an unstable value and illustrate one of the reasons why the EPA have preferred to use an UCL estimate rather than the central or 'best' estimate that many statisticians would prefer to report.

(2) q_1 is invariant despite the data*

The OTA[18] reported both that 'small fluctuations in the underlying data at high doses...can dramatically

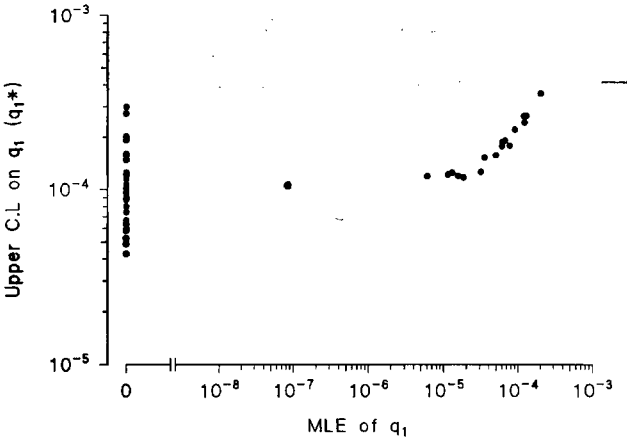


Figure 9 Plot of the MLE estimate, q_1, and the UCL, q_1*, of the slope from fitting the LMS model to a set of 50 simulated data sets. Each simulated experiment consisted of 4 log spaced doses, 50 animals per group with each group having a tumour incidence of 10% to simulate an experimental situation where there is no effect of the treatment.

change the maximum likelihood estimate at the low doses of interest' and that the 'upper confidence limit is a more stable number'. This stability is illustrated in Table 5, which shows two sets of hypothetical data (amongst the many that could be generated), where representative sets of data from a four group bioassay produce similar values of q_1*, although the biological or toxicological interpretation is likely to be quite different.

In both sets of data similar q_1* values are obtained with high dose effects, a monotonically increasing trend and an essentially negative result with no trend. Similar patterns can be seen in the other groupings in Table 5.

Table 6 shows a full range of values that can be obtained using the LMS model on data sets ranging from extreme negative to extreme positive trends, Values of q_1 range from zero to 1.41×10^{-2}.

Table 5 Data sets which illustrate the insensitivity of q_1* to the data in the study

Dose levels				
Control	*Low*	*Medium*	*High*	
0	*10*	*100*	*1000*	q_1*
2	4	6	8	2.43×10^{-4}
0	**0**	**0**	**50**	2.48×10^{-4}
14	**15**	**16**	**17**	2.80×10^{-4}
14	**[illegible]**	**[illegible]**	**[illegible]**	2.47×10^{-4}
0	**[illegible]**	**[illegible]**	**[illegible]**	2.32×10^{-4}
0	**0**	**1**	**[illegible]**	3.45×10^{-4}
3	**[illegible]**	**[illegible]**	**[illegible]**	3.43×10^{-4}
24	25	25	26	3.65×10^{-4}

q_1* is the 95% UCL estimate of the lifetime risk of cancer per unit dose. Table shows hypothetical sets of cancer bioassay data where numbers represent number of animals with a tumour in group sizes of 50 at each dose level. Dose levels for four groups (control, low, medium and high) are arbitrary units which could, for instance, represent mg/kg/day or ppm.

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Table 6 An illustration of the range of possible values of q_1 and q_1* across a range of values from extreme negative to extreme positive linear trends

Control	*Dose levels* *Low*	*Medium*	*High*	q_1	q_1*
0	*10*	*100*	*1000*		
50	34	17	0	0	2.63×10^{-5}
45	30	15	0	0	2.63×10^{-5}
30	20	10	0	0	2.63×10^{-5}
15	10	5	0	0	2.63×10^{-5}
3	2	1	0	0	2.62×10^{-5}
1	0	0	0	0	2.44×10^{-5}
0	0	0	1	0	6.37×10^{-5}
0	1	2	3	5.20×10^{-5}	1.42×10^{-4}
0	5	10	15	3.17×10^{-4}	5.23×10^{-4}
0	10	20	30	9.02×10^{-4}	1.28×10^{-3}
0	15	30	45	2.97×10^{-3}	4.13×10^{-3}
0	17	34	50	1.41×10^{-2}	1.93×10^{-2}

q_1 is the MLE estimate of the lifetime risk of cancer per unit dose. q_1* is the 95% UCL estimate of the lifetime risk of cancer per unit dose. Table shows hypothetical sets of cancer bioassay data where numbers represent number of animal with a tumour in group sizes of 50 at each dose level. Dose levels for four groups (control, low, medium and high) are arbitrary units which could, for instance, represent mg/kg/day or ppm.

Table 7 Data to show that the value of q_1* is dependent upon the top dose

Control	*Dose levels* *Low*	*Medium*	*High*	q_1	q_1*
(1/50)	*(7/50)*	*(9/50)*	*(14/50)*		
0	0.1	1	5	5.40×10^{-2}	9.16×10^{-2}
0	1.25	2.5	5	6.78×10^{-2}	9.65×10^{-2}
0	1.67	3.3	5	6.09×10^{-2}	8.52×10^{-2}
0	0.1	1	10	2.45×10^{-2}	4.33×10^{-2}
0	2.5	5	10	3.34×10^{-2}	4.82×10^{-2}
0	3.33	6.66	10	3.04×10^{-2}	4.26×10^{-2}
0	1	10	100	2.45×10^{-3}	4.33×10^{-3}
0	10	100	1000	2.45×10^{-4}	4.33×10^{-4}

q_1 is the MLE estimate of the lifetime risk of cancer per unit dose. q_1* is the 95% UCL estimate of the lifetime risk of cancer per unit dose. Table shows the q_1 and q_1* values obtained for a hypothetical set of cancer bioassay data (number of animals with tumour out of 50 treated shown in brackets below the respective dose level) representing a positive trend for different dose patterns. The table shows the different dose levels and the corresponding q_1 and q_1* values obtained for the representative bioassay data. Dose levels for the four groups (control, low, medium and high) are arbitrary units which could, for instance, represent mg/kg/day or ppm.

Estimates of q_1* cover 3 orders of magnitude from 2.63×10^{-5} for the extreme negative trend to 1.93×10^{-2} for an extreme positive trend. However, in the positive trends the range of values of q_1* is only just over 100-fold. This table also shows that a positive non-zero value of q_1* is given by the LMS model even when no tumors are reported, or even in extreme negative ('protective') cases.

In practice, the LMS model is only likely to be applied to data where a chemical has been identified or classified as a carcinogen. However, an appreciation that similar estimates of risk could also have been obtained from data which would have clearly been interpreted as a negative result may help to put any estimates of risk derived by the LMS model into perspective. For example, even if the 2, 3, 7, 8-TCDD study had produced a negative result, the LMS model would still have produced a q_1* value and given a RsD of about 0.7 pg/kg/day. The table also shows that in the range of results often observed in the LTRCB, such as from a small non-significant trend (0, 1, 2, 3) to a pronounced trend (0, 10, 20, 30), there is less than a 10-fold increase in q_1*.

(3) q_1 is closely related to the top dose*

The illustration of the application of the LMS model to 2, 3, 7, 8-TCDD suggested that the value of q_1* appeared to be influenced by effects at the top dose rather than at the lower doses. This is illustrated in more detail by the data in Table 7. A representative set of data is shown with different spacing or sizes of the doses. Changing the spacing of the doses but keeping the size of the top dose effect constant had little effect on the values of either q_1 or q_1*.

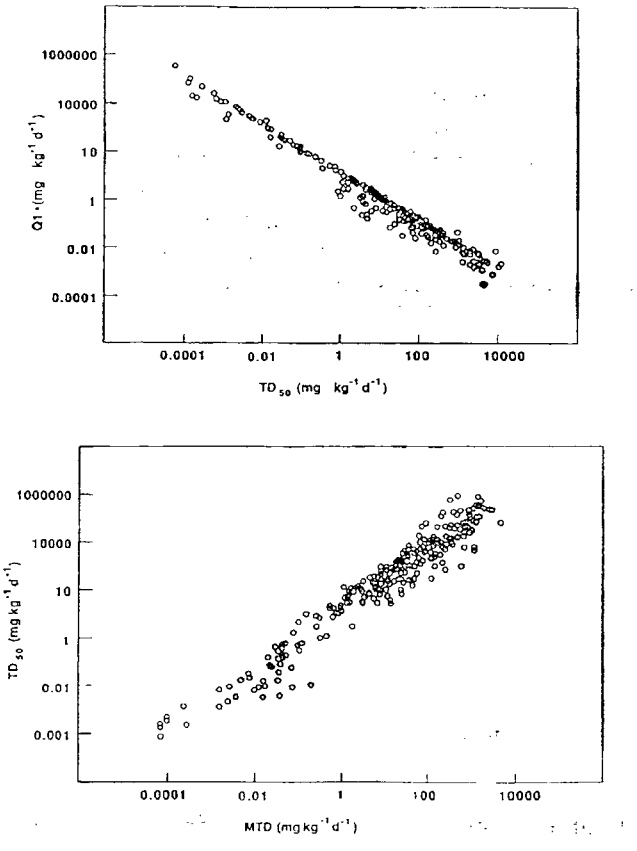


Figure 10 Correlation of q_1* and TD_{50} and of TD_{50} and the MTD as reported by Krewski D, Murdoch DJ & Withey JR. (1989) Dose-response models. Recent developments in carcinogenic risk assessment. *Health Physics* **57** 313–325 (Reproduced from Health Physics by permission of the author).

However, doubling the top dose effectively halved the values of q_1 and q_1* irrespective of the spacing of

the lower doses. The values of q_1 and q_1* are also an order of magnitude lower for every increase in the top dose by a factor of 10.

The relationship between the size of the top dose and the estimate of q_1* has been noted before. Krewski *et al*[37] have produced graphs (Figure 10) showing the association between the TD_{50}, a measure of carcinogenic potency as determined by Gold *et al*[38] and both the Maximum Tolerated Dose and q_1* based upon results from 263 chemicals in Gold *et al*'s database. The two figures reproduced show clearly that there would also be a high correlation (or association) between the MTD and q_1*. In other words, estimates of low dose potency used for estimating and ranking carcinogenic potency are closely related to the MTD, or at least to the top dose used in the LTRCB. The choice of the top dose for such studies is determined to a considerable extent by measures of toxicity detected in sub-chronic 90-day studies. The consequence is that estimates of cancer risk at low dose level obtained by using the LMS model may bear no relationship to the carcinogenic potential of the chemical. Kodell *et al*[39] have pointed out that this is a consequence of the limitations imposed by the choice of this particular model. The relevance of estimating the possible risks to humans from low dose exposures from the results produced at or near the MTD in rodent studies is debatable. This arises in particular because of the uncertainties likely to arise from factors such as differences in the absorption, distribution, metabolism and elimination of chemicals, and the activation, deactivation and repair mechanisms operating in different situations.

(4) q_1 becomes larger if the top dose data are excluded*

The relationship between the top dose and the value of q_1* has implications in those cases where data on the animals at the top dose are excluded for some reason. For instance, it may be considered that the increased tumour incidence obtained at the MTD or high doses was biologically or toxicologically irrelevant to the risks to humans at low doses. Alternatively, the top dose data may be excluded because the LMS model is a poor fit to the full data set based upon a chi-squared goodness of fit test.[9] In either case the value of q_1* resulting from applying the LMS model to the remaining data will probably be larger than that obtained by fitting the LMS model to the full data. A larger value of q_1* will be obtained irrespective of whether or not the remaining data show a statistically significant increased incidence in the treated groups.

This is illustrated in Table 8. The values of q_1 and q_1* increase by almost an order of magnitude when the top dose data of 1000 is excluded. The estimate of q_1* obtained would be *larger* and the estimates of VSD would be *smaller* than using the full data set.

A curious corollary would be that if the aim were to obtain the highest possible VSD using the LMS model for a chemical, then the optimum strategy might be to test at the highest possible dose, because of the inverse relationship between the top dose and the estimate of q_1*.

The implications of this property of the LMS model can be illustrated with the 2, 3, 7, 8-TCDD data used earlier. If the data sets used by the EPA and the FDA had excluded the top dose, then the q_1* values based upon the EPA's Pathologists (A and B) and FDA pathologist's diagnoses would have been 4.96×10^4, 8.52×10^4 and 4.69×10^4 $(mg/kg/day)^{-1}$, respectively. This would have resulted in VSD of 2.75×10^{-3} and 21.34×10^{-3} fg/kg/day for the EPA and FDA approaches, respectively. These values are approximately 50% lower than the values shown in Figure 8.

Table 8 Table to show the implications of dropping the top dose data for the fit of q_1 and q_1*

Control	*Dose levels*				
	Low	*Medium*	*High*		
0	*10*	*100*	*1000*	q_1	q_1*
0	5	10	15	3.17×10^{-4}	5.23×10^{-4}
0	5	10	N/A	2.29×10^{-3}	4.18×10^{-3}

N/A Not applicable. q_1 is the MLE estimate of the lifetime risk of cancer per unit dose. q_1* is the 95% UCL estimate of the lifetime risk of cancer per unit dose. Table shows a hypothetical set of cancer bioassay data where the numbers represent number of animals with a tumour in group sizes of 50 at each dose level. In the second line of data it was assumed that the top dose data were not considered appropriate for inclusion in the model (see text). Dose levels for four groups (control, low, medium and high) are arbitrary units which could, for instance, represent mg/kg/day or ppm.

Table 9 Table illustrating the relative insensitivities of q_1 and q_1* to changes in tumour incidence in the low dose groups

Control	*Dose levels*				
	Low	*Medium*	*High*		
0	*10*	*100*	*1000*	q_1	q_1*
0	5	10	15	3.17×10^{-4}	5.23×10^{-4}
0	4	10	15	3.34×10^{-4}	5.42×10^{-4}
0	6	10	15	3.02×10^{-4}	5.06×10^{-4}
0	5	9	15	3.19×10^{-4}	5.21×10^{-4}
0	5	11	15	3.14×10^{-4}	5.22×10^{-4}
0	5	10	14	2.84×10^{-4}	4.82×10^{-4}
0	5	10	16	3.51×10^{-4}	5.64×10^{-4}

q_1 is the MLE estimate of the lifetime risk of cancer per unit dose. q_1* is the 95% UCL estimate of the lifetime risk of cancer per unit dose. Table shows hypothetical sets of cancer bioassay data where numbers represent number of animal with a tumour in group sizes of 50 at each dose level. Dose levels for four groups (control, low, medium and high) are arbitrary units which could, for instance, represent mg/kg/day or ppm.

(5) Insensitivity of q_1 values to low dose data*
The small sensitivity analysis of the values of q_1* obtained using the EPA and FDA 2, 3, 7, 8-TCDD data suggested estimates of low dose carcinogenic potency using the LMS model were less affected by data from doses closer to the human exposure level than by data from the highest dose group. This is illustrated by another representative data set (Table 9). The numerators (number of animals with tumours) in the low, medium and top doses are altered by 1. However despite a disproportionate 20% increase or decrease at the low dose compared to a 6% change at the highest dose, there is a greater change in both q_1 and q_1* when the high dose data are changed. Such a change is, of course, contrary to the objective of the experimental design, in which it is hoped that information at the low dose range of the experiment would be more relevant to the slope of the dose-response relationship at even lower extrapolated doses.

(6) The VSD obtained from the LMS model is equivalent to the MTD/500000
Estimates of q_1* obtained from representative sets of data can be used to obtain approximate estimates of the degree of relationship between the MTD (or top dose) of a LTRCB and the VSD. Table 10 illustrates that for log spaced data (0, 10, 100, 1000) the estimates of q_1* for an extreme positive effect, a positive effect, a no-effect result and the extreme negative trend ('protective') result are of the order of 4.0×10^{-3}, 5.0×10^{-4}, 1.0×10^{-4} and 2.5×10^{-5}. These give MTD:VSD ratios of 4×10^6, 500 000, 100 000 and 25 000 respectively. (The corresponding ratios using the lowest level instead of the MTD would be 100 times smaller).

The majority of data selected for inclusion in a QRA are likely to be of the positive (but not extreme positive) type. Therefore, an approximate estimate of the VSD could be obtained by dividing the MTD, chosen as a consequence of the sub-chronic study, by 500 000.

The relationship between the MTD and the 10^{-6} VSD has previously been noted by Gaylor[40], who found that the mean ratio over 138 examples was 380 000. This relationship was discussed in more detail by Krewski *et al*[41] in the US National Research Council's CRAM report.[42]

Table 10 Table showing calculation of the ratio of MTD:VSD for four generalised types of LTRCB results

	q_1*	VSD	MTD:VSD
Extreme positive effect (0,15,30,45)	4.0×10^{-3}	0.00025	4,000,000
Positive effect (0,5,10,15)	5.0×10^{-4}	0.002	500,000
No effect (5,6,4,5)	1.0×10^{-4}	0.01	100,000
Extreme negative (protective) (50,34,17,0)	2.5×10^{-5}	0.04	25,000

Table shows the q_1*, VSDs values and the ratio of MTD:VSD associated with sets of data representative of different type of bioassay results – extreme positive, positive, no effect and extreme negative – assuming a four dose study with 50 animals per dose levels. Dose levels assumed to be logarithmically spaced (0, 10, 100 and 1000) in arbitrary dose units. The top dose (1000 units) is assumed for the purposes of illustration to be the Maximum Tolerated Dose (MTD).

Discussion

(1) Current use of the LMS model
The LMS model remains the EPA's default method for conducting QRA. Limitations of the model have been known for some time and the EPA has issued details of a review process for its carcinogenic risk assessment guidelines.[26] This process is now under way. Options for reviewing EPA guidelines have been prepared but have not been formally published.[43]

The present EPA guidelines[14] state:

'(I)n the absence of adequate information to the contrary, the linearized multistage procedure will be employed'

In practice this means that the LMS model will be used unless there is overriding evidence of an alternative and better approach. The model has also been adopted by the WHO for providing estimates for carcinogenic air contaminants for Europe.[44,45] These WHO Guidelines provide non-mandatory air quality guidelines for air pollutants in Europe. Estimates of q_1* are available in the EPA's IRIS database and are tabulated as Carcinogen Potency Factors (CPFs) in the ATSDR's 1990 Draft Health Assessment Guidance Manual. A modification of the LMS model has been used by the Californian EPA to produce q_1* values.[46] A listing of substances evaluated by the EPA's Carcinogen Assessment Group (CAG) together with estimates of slopes (i.e q_1* values) is also given by the OTA.[18]

Estimates of q_1* are also included in the non-binding health advisories for contaminants in water issued by the EPA under the US Safe Drinking Water Act.[18] The CPFs are also used by the EPA as part of its hazard ranking for substances under 'Superfund' legislation in the US.

The association between the values of q_1* and the TD_{50} is not surprising, as the mathematical modelling underlying the TD_{50} is a one-hit model, and there is a high correlation between estimates obtained from the one-hit and multi-stage models (see Figure 2). The one-hit model suffers from the same problem that the estimate of the slope is highly influenced by the top dose.[39]

(2) The conservatism of the LMS model
The LMS model, therefore, appears flawed or at

least severely limited. The conservative assumptions underlying the model have been stressed on a number of occasions. These assumptions include the choice of the most sensitive species, sex and site; the combination of benign and malignant tumours; acceptance of a no-threshold model, and the failure to distinguish between genotoxicity and non-genotoxicity or other relevant mechanistic information. In addition, the LMS model is a conservative model with the assumption of linearity and the choice of the upper confidence limit both providing overestimation to an unknown degree of every risk estimate. Each of these assumptions will result in an overestimate of a risk. The use of a species conversion factor may also add a further degree of conservatism.

The EPA[14] has recognized the conservatism of the LMS approach by describing the estimates obtained by stating:

'Such an estimate [based on the upper confidence limit] . . . does not necessarily give a realistic prediction of the risk. The true value of the risk is unknown, and may be as low as zero. The range of risks, defined by the upper limit given by the chosen model and the lower limit which may be as low as zero, should be explicitly stated'

The true risk may, therefore, be extremely small and could be practically zero (to allow for there being no concept of absolute safety or zero risk) and, thus, inconsequential.

The degree of overestimation (or conservatism) is unknown, although estimates have been made of the range of possible overestimation as a consequence of the various assumptions. The implication is that an estimate of risk is obtained by dividing a dose level producing an effect in animals by a large but ill-defined (and unknown) factor. Extremely precise estimates of risk can be obtained, although the EPA now recommend no more than 1 significant figure is reported[14,18], but these estimates can have wide ranges of errors. They are consequently precise but not necessarily accurate. In the examples presented in this paper, estimates of the q_1, q_1^* and VSD values are presented with up to three significant figures, so that the effects of changes in the data can be illustrated.

There is still controversy over whether the 'best' estimate (which may actually be zero or very close to zero) should be used or whether the UCL should be used. The inaccuracies in the estimates of risk identified here suggest that attempts to prioritise actions based upon these estimates (which for animal data are closely related to the MTD) are likely to be inappropriate.

Further conservatism is introduced into the assessment of exposure when the average and extreme estimates of exposure or intake are derived. Exposures based upon the maximum possible exposure using all the pathways of the most susceptible individuals over the individuals' lifetime add a further set of ill-defined factors adding to overestimation of risk.

Regulatory authorities usually have a responsibility to protect health and maintain a safe environment and are, therefore, likely to incline to the side of safety and adopt conservative assumptions in their risk management procedures. However, there are considerable complexities in the communication of the uncertanties in risk assessment between risk assessors and risk managers, and it is not always clear that these assumptions have always been appreciated by risk managers. The choice of the assumptions made by the risk assessor, in fact, means that decisions regarding the size of the risk are being made by the scientist rather than the risk manager as the split in the two processes was envisaged by such organisations as the NAS. In other words, the risk assessor, by using 'worst-case', overly conservative estimates of risk to provide a science-based risk assessment, is introducing subjective or value judgments of the level of acceptable risk, which should be the role of the risk manager. The risk assessor is, therefore, defining and determining a risk-averse approach to QRA.

(3) Alternative approaches to the LMS model

Alternative approaches to the use of the LMS model have included other mathematical models and non-parametric approaches. The other mathematical models share many of the same problems of the LMS model, while some of the suggested non-parametric approaches produce similar estimates of risk to those produced by the LMS model.[47] In effect, the LMS model is equivalent to a standard that alternative approaches are 'tested' against.

Moves to develop physiologically-based pharmacokinetic (PB-PK) models, biologically-based dose-response (BB-DR) models or receptor based models should eventually produce more accurate estimates of risk at low doses in animals and, in some cases, may provide some confidence in extrapolation of the results from animals to humans. It is important, however, to appreciate that while the use of PB-PK models may provide more realistic measures of the dose delivered to the target organs they do not correct the limitations of the LMS model.

Development of surrogate measures of toxicological events, such as biomarkers like DNA and protein adducts or receptor-binding, may allow investigation of dose-response relationships at lower doses. These may help extrapolation by allowing experimentation at doses closer to human exposures. There will remain, however, questions about the relevance of some of these biomarkers to the development of toxic injuries.

These developments in the integration of mathematical modelling with molecular events offer the

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hope of providing more accurate quantitative information about the risks posed by individual chemicals. However, it is unlikely that such developments will provide an approach which will provide similar rankings to those based upon applying the LMS model to the LTRCB database to produce lists of q_1* values.

Problems with the LMS model have previously been pointed out by Sielken[48], Gaylor[40], Johannsen[49] and Krewski *et al.*[50] Both Sielken and Johannsen have pointed out that estimates of q_1* can be obtained for data where there is either no evidence of a trend or the trend is negative.

The consequence of estimates of risk derived from q_1* is that action based upon these estimates may be inappropriate, and there is the danger of a mis-allocation of resources to reduce exposures below what is believed, based on the estimate of q_1*, to be a 10^{-6} level. Such estimates could, in fact, be seriously biased.

Conclusions

The Linearized Multistage (LMS) model has provided a convenient model for use within the US regulatory framework. It involves fitting the multistage model as a polynomial equation and using the linear component of the polynomial, q_1, to carry out low dose extrapolation. The linear component is equivalent to the slope of the dose-response relationship at low doses. The best fitting or Maximum Likelihood Estimate (MLE) slope, q_1, or the steeper 95% Upper Confidence Limit, q_1*, values are usually used for the low dose extrapolation to obtain, for instance, the dose associated with a specific increased risk of 10^{-6}, often called the 'Virtually Safe Dose (VSD)'.

Analysis of data using the LMS model showed (i) that the MLE value, q_1, was unstable and extremely sensitive to small changes in the data; (ii) the UCL value, q_1*, preferred by the US EPA, was insensitive, with only small changes in values being obtained for large changes in the data; (iii) data sets where there was no statistical significance could give results similar to those obtained with clear dose-related effects; (iv) the size of the values of the VSD obtained did not necessarily relate to the biological interpretation of the data sets; (v) the value of q_1* obtained was closely related to the top dose used in the study and was much less influenced by data in the low dose region.

The majority of data sets currently available for inclusion in QRA are quantal data, such as the proportion of exposed animals showing a tumour. The use of such data in the LMS model probably results in a large and indeterminable overestimate of the risk to the human population. The method chosen by the US EPA is deliberately conservative; the true risk is likely to be very much lower than that reported. The degree of conservatism, however, is unknown, difficult to estimate and is hidden by the methodology used.

The use of the LMS model has been justified in part by its original derivation from a mathematical model based upon a multistage model of carcinogenesis. However, the LMS model seems to provide a narrow range of VSDs, which are largely determined by the doses used in the study and only to a lesser extent by the actual results obtained in the experiment. The other quantal models are open to similar criticism. The LMS approach represents a way to obtain quantitative risk estimates. However, these estimates are likely to be highly conservative to an indeterminate degree, estimates of the parameters of the model have no direct relationship to specific biological event in carcinogenesis, have little biological relationship to the actual data collected, and will produce risk estimates which are potentially biased and distorted. The approach represents a valiant but nevertheless flawed attempt to solve a pressing problem.

The results of the studies reported here show that the estimates of the risks to the human population associated with low levels of exposure to chemicals derived by using the Linearized Multistage Model are unreliable and scientifically unsound.

It is concluded that QRA based upon mathematical modelling using the LMS model is inappropriate unless a regulatory system requires a numerical estimate of risk and is prepared to accept inaccurate estimates, which probably have a high but unknown level of in-built conservatism. In the future, further developments in mathematical models and increasing understanding of the biological events underlying carcinogenesis may lead to more biologically plausible QRA methods. Such advances would then justify serious consideration of QRA by regulatory authorities throughout the world.

Acknowledgements

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March 12, 2007

The Honorable Anthony J. Mohr
Judge of the Superior Court
Department 309
Los Angeles County Superior Court
Central Civil West Courthouse
600 S. Commonwealth Avenue
Los Angeles, CA 90005

RE: *Environmental Law Foundation v. Birds Eye Foods, Inc., et al.*
Los Angeles Superior Court Case No. BC356691

Dear Judge Mohr:

As indicated in our letter of February 25, 2007, we have received the transcript of the Court's hearing on defendants' demurrer in this matter, in which the Court stated that it would like to hear the Attorney General's views on the pending issues. As we understand it, the issue is as follows: Given that Proposition 65 bars a private party from filing an enforcement action where the Attorney General "has commenced and is diligently prosecuting an action against the violation," does the Attorney General's identification of Doe defendants in his complaint concerning acrylamide in french fries and potato chips bar an action by a private party against defendants who are not specifically identified in the Attorney General's complaint?

A. Procedural History

On August 26th, 2005, the Attorney General filed a complaint in *People v. Frito-Lay, et al.* (Los Angeles Superior Court No. BC 338956. In this complaint, the Attorney General identified eleven defendants, each of whom is alleged to have violated Proposition 65 by failing to warn consumers of the presence of acrylamide, a chemical known to the state to cause cancer, in certain products. None of the specifically named defendants are defendants in the current action pending in this Court. The products are identified as "Lay's potato chips, Lay's potato crisps, Kettle Chips, Cape Cod potato chips, Pringles potato chips, frozen potato products sold by H.J. Heinz, french fries sold by Wendy's International, french fries sold by McDonald's Corporation, french fries sold by Burger King Corporation, and "Potato Wedges" sold by KFC

Corporation (hereinafter 'the Potato Products')[.]" (Complaint, Par. 27.)[1]

In addition to the specifically identified defendants, the Attorney General's complaint alleges the existence of Doe defendants, stating that the "true names and capacities of the defendants sued herein as Does 1 through 100 are unknown to plaintiff" and that "[e]ach of the fictitiously named defendants is responsible in some manner for the conduct alleged herein." (Complaint, Par. 14.)

That action, and the remaining actions by the other private plaintiffs, are pending before Judge Mortimer.

In the case before this Court, plaintiff Environmental Law Foundation filed its complaint on August 8, 2006, naming as defendants Birds Eye Foods, Inc., and nine other business entities (as well as 100 Doe defendants). None of the defendants identified in the Environmental Law Foundation complaint are named defendants in the People's complaint. The complaint was preceded by a sixty-day notice of violation against those companies and others, on May 24, 2006.

Defendants demurred, arguing that the identification of Doe defendants who sell potato products in the People's complaint means that the People have "commenced and diligently prosecuted an action against the violation" with respect to the defendants identified in Environmental Law Foundation's complaint, and therefore Environmental Law Foundation's action is barred.

B. Statutory Language

Health and Safety Code Section 25249.6 provides that "no person in the course of doing business shall knowingly and intentionally expose any individual to a chemical known to cause

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[1]Before the Attorney General filed suit, two private groups had filed four different suits against the same defendants, three of which are still pending: *Council for Education and Research and Education on Toxics v. McDonald's Corporation and Burger King Corporation* (Los Angeles Sup. Ct. No. BC 280980), *Environmental World Watch, Inc. v. the Procter & Gamble Distributing Company, et al.* (Los Angeles Sup. Ct. No. 337618), and *Environmental World Watch v. H.J. Heinz Company* (Los Angeles Sup. Ct. No. 337619). Since Proposition 65 does not preclude the Attorney General from filing a suit after a private party has filed one, the existence of those complaints do not affect the Attorney General's action. Their existence also is not relevant to the issue before this Court in this matter.

cancer or reproductive toxicity without first giving clear and reasonable warning[.]"[2] Thus, the violation consists of a person being exposed to the chemical without a proper warning being given (or one of the exemptions being established), for example by using a consumer product. This one "violation," however, may be caused by more than one "violator." Each entity in the chain of distribution causes the exposure by making or selling the product, and may be responsible for the violation if it meets the other requirements of the law, e.g., it has knowledge of the exposure to the chemical, the exposure is the result of an intentional act, and it is not otherwise exempt. For example, suppose Manufacturer makes a potato chip containing a chemical which it knows contains a chemical known to the state to cause cancer, it is distributed through Distributor, and sold at retail by Retailer. The sale of the potato chip would constitute one violation of the statute. Because each party, Manufacturer, Distributor, and Retailer, caused the exposure to the chemical, each is a violator (assuming that they know that the chemical is present and are not otherwise exempt from the law). Thus, a number of individual violators may contribute to a single violation.

Under Proposition 65, the Attorney General may prosecute an action "in the name of the People of the State of California" without limitation. (§ 25249.7, subd. (c).) A private party may file suit "in the public interest," but only where certain conditions are met. In order for a private party to file suit, it first must have "given notice of an alleged violation...that is the subject of the private action[.]" (§ 25249.7, subd. (d)(1).) The notice must be provided to the Attorney General and any district attorney in whose jurisdiction "the violation is alleged to have occurred, and to the alleged violator." (*Id.*) In addition, no suit may be filed if a public prosecutor "has commenced and is diligently prosecuting an action against the violation." (§ 25249.7, subd. (d)(2).)

The distinction between "violation" and "violator" is one of substance. The private party's notice must identify both the violation and the particular violator, and its suit is limited to the violation and the violator identified in the notice.[3] A given violation may be caused by more than one violator, but the private party can sue only those violators it has identified in its notice. In contrast, the public prosecutor's suit bars the private suit wherever it addresses "the violation," i.e., the violation alleged in the sixty-day notice. Thus, if a private party were to provide a notice alleging that Company A manufactured product X, but also identifying Retailer B as a violator, it

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[2]All statutory citations are to the Health and Safety Code, unless otherwise indicated.

[3]Regulations governing the text of the sixty-day notice prescribe how the "violation" must be identified as well as how the "violator" must be identified and served. (Cal. Code Regs., tit. 22, § 12903, subd. (b)(2) [description of violation], (b)(2)(A)2 [identification of violator], (b)(2)(D) [description of consumer product].

could sue both companies over that product. If the Attorney General, however, were to file a suit concerning the sale of product X against Company A, the action is "against the violation" and precludes a private party from suing other violators for the same violation, even if they are not identified in the Attorney General's suit. The private party therefore could not file suit against Retailer B with respect to the products identified in the Attorney General's suit.

C. Effect of the Doe Allegations

Doe allegations, such as those contained in the Attorney General's complaint, are permissible where the plaintiff is not aware of the identities of the defendants. (See Code Civ. Proc., § 474; Witkin, 4 California Procedure at p. 531 [Pleadings, § 439].) Doe allegations also are permitted where the plaintiff is aware of the identity of the defendant, but not of the facts giving rise to liability. (*Id.*, at p. 540 (Pleading, § 445); *General Motors v. Superior Ct.* (1996) 48 Cal.App.4th 580, 593-594, 597.)

When the Attorney General filed his complaint on August 26, 2005, he did not necessarily know of the identities of the defendants in the Birds Eye case, or of the facts constituting the cause of action against them. By virtue of receipt of the notices of violation from Environmental Law Foundation on May 24, 2006, the Attorney General became aware of the identities of the defendants, and the facts constituting the cause of action.

We do not think, however, that the inclusion of Doe defendants in the August 26, 2005 complaint means that the Attorney General had "commenced and diligently prosecuted an action" against any specific violation other than the violations for products identified specifically in the complaint. Where neither the specific product, or manufacturer, distributor, or retailer of that product have been identified in the complaint, no relief could be obtained against those parties, and no discovery could be commenced against them. They are not within the jurisdiction of the Court, and are not bound by any judgment entered in the case, until they are served with a summons and complaint. (Witkin, *supra*, at p. 547 (Pleading § 449).) Under those circumstances, we do not think an action against "the violation" has been commenced, nor do we think the Attorney General could be considered to be "diligently prosecuting" an action against the violation with respect to those entities who are not selling products otherwise identified in the Attorney General's complaint.[4]

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[4]Theoretically, if one of the defendants in this matter *also* distributes or sells some of the products specifically identified in the Attorney General's complaint, e.g., Lay's Potato Chips, then the Attorney General's action against that violation bars any action by Environmental Law Foundation with respect to those products (regardless of any Doe allegations). Nothing on the face of the record indicates that this is true, however.

Of course, if the Attorney General were to identify and serve any of the Doe defendants in this case, then he would have "commenced and diligently prosecuted an action against the violation" with respect to those defendants and their products. If a private party had not already filed suit, then such a suit would be precluded. If the private party already had filed suit against those defendants, the Attorney General's action still could proceed, because the statute does not provide that a private action ever bars an action by the Attorney General.[5]

In summary, we think that where the Attorney General has sued one or more parties, such as the manufacturer, distributor, and retailer of the identical product, the Attorney General has commenced an action against the "violation," which precludes a private action against the named defendant and any other violators who sold the identical product, including any other party in the chain of distribution. We do not think, however, that the identification of Doe defendants who have sold a generally described product in a complaint, without more, means that the Attorney General has "commenced and diligently prosecuted an action against such violation."

D. Case Management Issues

The issue of whether a demurrer to the complaint must be sustained differs from the issue of how a court should manage such cases, where they raise similar issues, some of which may be resolved in the Attorney General's action. Such matters often are considered by courts in the context of efficient case management, related cases, or coordination petitions. The Court also may wish to consider the Attorney General's important role in Proposition 65 in considering the appropriate methods of case management. We did not understand the Court to have requested the Attorney General's views on such issues, however, and we therefore are not providing them.

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[5]Identification of Does also could raise other issues concerning whether the relatively narrow Doe allegations apply to those parties, whether the defendants were prejudiced by delay in identifying them in the complaint, and how to apply the "relation back" doctrine in considering whether the private plaintiff's action is precluded. None of those issues is presented on the pending demurrer.

If the Court concludes that the Attorney General can in any way assist the Court by providing information concerning the status of the other acrylamide cases, however, we will be happy to respond.

Respectfully submitted,

Edward Weil/BB

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cc: all counsel, per attached proof of service

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SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF LOS ANGELES, CENTRAL CIVIL WEST

COUNCIL FOR EDUCATION AND RESEARCH ON TOXICS, a California corporation, acting as a private attorney general in the public interest; Plaintiff, vs. STARBUCKS CORPORATION, a Washington corporation; et al., Defendants.	CASE NO. BC435759 Consolidated with Case No. BC461182 *Assigned to the Honorable Elihu Berle, Dept. 323* **PLAINTIFF'S TRIAL BRIEF REGARDING THE DETERMINATION OF CIVIL PENALTIES FOR VIOLATION OF PROPOSITION 65** TRIAL DATE: August 28, 2017 TRIAL TIME: 9:00 a.m. DEPARTMENT: 323

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1. PRELIMINARY STATEMENT

This memorandum addresses the "damages" issues in this case, i.e., the amount of civil penalties that should be imposed against Defendants for their numerous violations of the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65).

Determination of the amount of civil penalties involves two essential issues: (1) determining the number of violations of Proposition 65 and (2) determining the amount of the penalty that should be imposed for each violation.

Proposition 65 provides for recovery of civil penalties not to exceed $2,500 per violation and is cumulative to other penalties allowed by law. Health & Safety Code § 25249.7(b).

California law is well-established that once plaintiff proves its prima facie case (which the court has already summarily adjudicated in Plaintiff's favor against all but two defendants), the burden is on Defendants to prove, by a preponderance of the evidence, that less than the maximum penalties should be imposed against them. *State of California v. City and County of San Francisco* (1979) 94 Cal. App.3d 522, 530-532. See, also, *Rich v. Schwab* (1998) 63 Cal.App.4th 803, 817.

Therefore, the court should adopt the following procedure in determining civil penalties against defendants: First, determine the number of Proposition 65 violations committed by the defendant. Second, presume that the maximum penalty of $2,500 per violation should be assessed against the defendant. Third, if the court admits evidence proffered by defendant in mitigation of penalties, reduce the amount of penalties against defendant as the court deems proper.

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2. THE TOTAL NUMBER OF PROPOSITION 65 VIOLATIONS IS DETERMINED BY MULTIPLYING THE NUMBER OF INDIVIDUALS A COMPANY EXPOSES TO A CARCINOGEN OR REPRODUCTIVE TOXIN PER DAY TIMES THE NUMBER OF DAYS OF EXPOSURE

Health & Safety Code § 25249.7(b)(1) states as follows:

> Any person who has violated Section 25249.5 or Section 25249.6 shall be liable for a civil penalty not to exceed $2500 ***per day for each such violation*** in addition to any other penalty established by law. . . . (Emphasis added)

Health & Safety Code § 25249.6 states:

> No person in the course of doing business shall knowingly and intentionally ***expose any individual*** to a chemical known to the state to cause cancer or reproductive toxicity without first giving clear and reasonable warning to such individual, except as provided in Section 25249.10. (Emphasis added)

Collectively, these statutory provisions establish that penalties for violation of the warning requirement of Proposition 65 must be assessed "for each such violation" (i.e., for "expos[ing] any individual") and that such penalties must be assessed "per day" (i.e., every day that individuals are exposed).

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This conclusion is not only clear from the plain meaning of the statute; it is also supported by case law.

Thus, in a deceptive advertising case, it was held that the trial court did not err in assessing a penalty under the Unfair Competition Act on a "per victim" basis, i.e., by using number of sales made by deceptive methods to calculate number of corresponding violations for purposes of assessing fine. *People v. Toomey* (1984) 157 Cal.App.3d 1, 203 Cal.Rptr. 642.

Likewise, where deceptive advertising occurred by publication of a newspaper advertisement, it was held that a trial court properly reasoned that a single publication constituted a minimum of one violation with as many additional violations as there were persons who read advertisement or who responded to the advertisement by purchasing advertised product or service or by making inquiries concerning the product or service. *People v. Superior Court* (1979) 96 Cal.App.3d 181, 157 Cal.Rptr. 628.

3. THE BURDEN OF PROVING THAT LESS THAN THE MAXIMUM PENALTY OF $2500 PER VIOLATION PER DAY SHOULD BE ASSESSED IS ON DEFENDANTS - NOT ON THE PLAINTIFF

Where the plaintiff proves that the defendant has violated an environmental statute that specifies a maximum civil penalty, the burden of proof shifts to the defendant to establish, by a preponderance of the evidence, that the amount of the penalty should be less than the maximum. *State of California v. City and County of San Francisco* (1979) 94 Cal.App.3d 522, 530-532. See, also, *Rich v. Schwab* (1998) 63 Cal.App.4th 803, 817.

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"Where . . . the Legislature has set the level of punishment which may be imposed for a particular act, the doctrine of separation of powers limits the nature of . . . review when such a penalty has in fact been imposed. [Appellate courts] are required to 'accord substantial deference to legislative judgments concerning appropriate sanctions for the conduct at issue.'" *Rich v. Schwab* (1998) 63 Cal.App.4th 803, 816, quoting, *BMW of North America, Inc. v. Gore* (1996) 517 U.S. 559, 583. "As with any other statute, [appellate courts] may interfere with the Legislature's determination of what is required by the public interest only when there is no rational basis for the decision reached by [the] Legislature." *Rich v. Schwab, supra,* 63 Cal.App.4th at 816, citing, *Horezcko v. State Bd. of Registration* (1991) 232 Cal.App.3d 1352, 1358.

7. CONCLUSION

The court should determine the presumptive amount of civil penalties by multiplying the number of violations of each defendant by $2,500. The court should impose this amount of penalties against defendants unless they offer admissible mitigating evidence that persuades the court to assess a lesser amount of penalties. In doing so, the court should not consider any constitutional limitations, as such limitations are not applicable to statutory civil penalties.

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