Comments on IRIS Toxicological Review of Benzo(a)pyrene

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Sponsors

- American Coke and Coal Chemicals Institute
- American Fuels & Petrochemical Manufacturers
- American Petroleum Institute
- Asphalt Institute
- Association of American Railroads
- Beazer East, Inc.
- Pavement Coatings Technology Council

Agenda

- Skin cancer hazard identification
  - Coal tar pharmaceutical & OTC product users
  - Human skin grafts on mouse skin
- Dermal slope factor (DSF)
  - Lack of real world recommendations
  - DSF recommendations

Agenda, con't

- Lung cancer hazard identification
- Inhalation unit risk factor (IUR)
  - IUR recommendations
- Inhalation reference concentration (RfC)
  - RfC recommendations
- Oral slope factor (OSF)
  - OSF recommendations
- Oral reference dose (RfD)
  - RfD recommendations

Skin Cancer Hazard Identification

Skin Cancer Hazard Identification

- 12 studies cited
- 7 studies negative
- 5 studies irrelevant or inconclusive
- 1 study review article of historical chimney sweep cancer reports
- Chimney sweep skin cancer unique to England, massive doses, not relevant to 21st century hazard identification

Summary of Reports Cited by USEPA (2013) Alleging Human Skin Cancer

Citation	Worker Group	Studied Effect Reported by USEPA (2013)	Statistical Significance Reported by USEPA (2013)	Actual Reported Statistical Significance
Spinelli et al. (2006)	Aluminum	Melanoma	Not significant	Not significant
Gibbs et al. (2007a,b)	Aluminum	Melanoma	Not significant	Not significant
Brown and Thornton (1957)	Chimney Sweeps	Scrotal cancer	Not reported & irrelevant	Not reported & irrelevant
Hammond et al. (1976)	Roofers/Water-proofers	Non melanoma skin cancer	Significant	Not significant
Pukkala (1995)	Round-timber workers	Non melanoma skin cancer	Significant	Not relevant*
Karlehagen et al. (1992)	Creosote wood treatment workers	Non melanoma skin cancer	Significant	Not relevant*
Tornquist et al. (1986)	Power linesmen	Non melanoma skin cancer	Not significant	Not significant
Roelofzen et al. (2010)	Coal Tar Pharmaceutical Users	Non melanoma skin cancer	Not significant	Not significant
Pittlekow et al. (1981)	Coal Tar Pharmaceutical Users	Non melanoma skin cancer	Not significant	Not significant
Maughan et al. (1980)	Coal Tar Pharmaceutical Users	Non melanoma skin cancer	Not significant	Not significant
Stern et al. (1998)	Patients Exposed to Carcinogenic Psoralens	Non melanoma skin cancer	Not reported	Not relevant*
Stern et al. (1980)	Patients Exposed to Carcinogenic Psoralens	Non melanoma skin cancer	Not reported	Not relevant*

Errors Regarding Skin Cancer

- Hammond et al. (1976) reported as significant
  - Study did not perform significance testing
  - IARC (2013) reports non-significant SMR of 0.8 to 11.7
- Pukkala (1995) reported as creosote workers
  - Study is about timber, not creosote workers
- Stern et al. (1980, 1998) reported as significant
  - Studies irrelevant because of exposures to carcinogenic psoralens

IARC Reports

- EPA (2013) cites IARC & IARC discusses selected mixtures
  - Coal tar distillation
  - Creosotes
  - Soot (chimney sweeping)
- BaP is not implicated in the mixture epidemiology

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IARC: Coal Tar Distillation

- Henry (1946)
  - Survey paper, not epidemiology
  - Not “coal tar” as stated by IARC; paper attributes to “pitch, tar, and tar-products”
- Letzel & Drexler (1998)
  - Retrospective survey, not epidemiology
- Both: no exposure information

IARC: Creosotes

- O'Donovan (1920): case report (n=4)
- Cookson (1924): case report (n=1)
- Henry (1947): case report (n=34)
- Henry (1946): irrelevant, refers to "brickmakers"
- Neither IARC nor EPA cite Wong and Harris (2005)
  - 2,199 creosote workers at 11 plants
  - Negative study

IARC: Soot (Chimney Sweeping)

Citation	Notes/Observations
Pott (1775)	Lecture, not epidemiology
Earle (1808)	Case report
Butlin (1892)	Lecture explains that “sweep’s cancer of the scrotum is a disease which is almost unknown in the large European countries and in the United States of America.”
Henry and Irvine (1936)	Survey report
Henry (1937)	Survey report
Henry (1946)	No data on chimney sweeps
Henry (1947)	No data on chimney sweeps
Evanoff et al. (1993)	No increase in cancer in sweeps
Pukkala (1995)	No increase in cancer in sweeps

Coal Tar Pharmaceutical Studies

- EPA's bibliography totally ignored coal tar pharmaceutical users
- Commenters sent bibliography to EPA
- EPA (2013) cited 3 of 20 studies & did not use the full weight of evidence
- FDA does not seem to have provided its opinion during Interagency Commenting
- Most recent study - Roelofzen et al. (2010)
  - 13,200 psoriasis and eczema patients
  - 8,062 received coal tar treatments
  - No increase in risk of: Skin cancer, all cancer, internal cancer, cancer of specific sites

Summary of Epidemiological Studies and Review Articles on the Use of Coal Tar Containing Pharmaceuticals (1/5)

Author	Date	Study Population	Conclusion Of Report	Notes Regarding Coal Tar As A Risk Factor
MacKenna (Mackenna RMB, 1959, Uncomplicated Psoriasis, Br Med J, Dec, 1959, 244-1247)	1959	No specific population studied	Adverse effects are rare	Review article concludes that coal tar does not increase risk of skin cancer
Muller and Kierland (Muller SA, Kierland RR, 1964, Crude Coal Tar in Dermatologic Therapy, Mayo Clin Proc, 39, 275-280.)	1964	123 patients treated with coal tar + UV for 38 years	No evidence of adverse effects	Concludes that coal tar is efficacious and safe
Perry et al. (Perry HO, Soderstrom CW, Schulze RW, 1968, The Goeckerman Treatment of Psoriasis, Arch Dermatol, 98, 178-182)	1968	123 patients treated with coal tar + UV for 38 years	No evidence of adverse effects	Concludes that coal tar is efficacious and safe
Epstein (Epstein JH, 1979, Risks and Benefits of the Treatment of Psoriasis, New England J Med, 300(15), 852-853)	1979	No specific population studied	Adverse effects are rare despite 50 years of use	Review article concludes that coal tar is not a risk factor for skin cancer.

Summary of Epidemiological Studies and Review Articles on the Use of Coal Tar Containing Pharmaceuticals (2/5)

Author	Date	Study Population	Conclusion Of Report	Notes Regarding Coal Tar As A Risk Factor
Maughan et al. (Maughan WZ, Muller, SA, Perry HO, Pittelkow MR and O'Brien PC, 1980, Incidence of Skin Cancers in Patients with Atopic Dermatitis Treated with Coal Tar, Am Acad Dermatol, 3(6), 612-615)	1980	426 patients with atopic dermatitis who received coal tar/UV therapy	Skin cancer was not increased above expected incidence for unexposed populations after 25 years	Concludes that use of coal tar did not increase risk of skin cancer
Pittelkow et al. (Pittelkow MR, Perry HO, Muller SA, Maughan WZ and O'Brien PC, 1981, Skin Cancer in Patients With Psoriasis Treated With Coal Tar, Arch Dermatol, 117, 465-468.)	1981	280 psoriasis patients who received coal tar/UV therapy	Skin cancer was not increased above expected incidence.	Concludes that use of coal tar did not increase risk of skin cancer
Muller et al. (Muller SA, Perry HO, Pittelkow MR, Maughhan WZ, O'Brien PC, 1981, Coal Tar, ultraviolet Light, and Cancer, J Am Acad Dermatol, 4(2), 234-235.)	1981	Patients receiving coal tar/UV treatment	Skin cancer was not increased above expected incidence for unexposed populations	No increase in skin cancer; same patients as in Maughan et al., 1980 and Pittelkow et al., 1981
Bickers (Bickers DR, 1981, The Carcinogenicity and Mutagenicity of Therapeutic Coal Tar - A Perspective, J Invest Dermatol, 77, 173-174)	1981	No specific population discussed	Review article concludes that coal tar is not a risk factor for skin cancer	Review article concludes that coal tar is not a risk factor for skin cancer

Summary of Epidemiological Studies and Review Articles on the Use of Coal Tar Containing Pharmaceuticals (3/5)

Author	Date	Study Population	Conclusion Of Report	Notes Regarding Coal Tar As A Risk Factor
Menter and Cram (Menter A and Cram DL, 1983, The Goeckerman Regimen in Two Psoriasis Day Care Centers, J Am Acad Dermatol, 9, 59-65.)	1983	300 psoriasis patients receiving coal tar/UV treatment	No increase in skin cancer compared to expected rates in general population	No increase in skin cancer, although follow-up was short.
Alderson and Clarke (Alderson MR, and Clarke JA, 1983, Cancer Incidence in Patients with Psoriasis, Br J Cancer, 47, 857-859.)	1983	8,405 psoriasis patients with no specific information on treatments	No increase in skin cancer compared to expected rates in general population	Supports conclusion that coal tar does not increase risk of skin cancer, because many patients can be presumed to have received coal tar treatment
Muller and Perry (Muller, S.A. and Perry, H.O. 1984. The Goeckerman Treatment in Psoriasis: Six Decades of Experience at Mayo Clinic. Cutis. 34. 265-269.)	1984	280 psoriasis patients who received coal tar/UV therapy	Skin cancer was not increased above expected incidence.	Concludes that use of coal tar did not increase risk of skin cancer
Lin and Moses (Lin AN, Moses K, 1985, Tar Revisited, Int J Dermatol, 24, 216-218.)	1985	135,000 psoriasis patients	In a survey of 90 dermatologists, only 3 reported skin cancer cases in psoriasis patients	Supports conclusion that coal tar does not increase risk of skin cancer

Summary of Epidemiological Studies and Review Articles on the Use of Coal Tar Containing Pharmaceuticals (4/5)

Author	Date	Study Population	Conclusion Of Report	Notes Regarding Coal Tar As A Risk Factor
Jones et al. (Jones SK, Mackie RM, Hole DJ, Gillis CR, 1985, Further Evidence of the Safety of Tar in the Management of Psoriasis, British Journal of Dermatology, 113, 97-101.)	1985	719 psoriasis patients receiving coal tar therapy only (no psoralens, cytotoxic drugs or UV-B)	No increase in skin cancer seen compared to general population	Supports conclusion that coal tar does not increase risk of skin cancer
Torinuki and Tagami (Torinuki W, Tagami H, 1988, Incidence of Skin Cancer in Japanese Psoriatic Patients Treated with Either Methoxsalen Phototherapy, Goeckerman Regimen, or Both Therapies, J Am Acad Dermatol, 18, 1278-1281.)	1988	43 psoriasis patients who received coal tar/UV therapy	No skin cancers reported.	Supports conclusion that coal tar does not increase risk of skin cancer, although numbers are small and follow-up was short
Lindelof and Sigurgeirsson (Lindelof B, Sigurgeirsson B, 1993, PUVA and Cancer: A Case-Control Study, Br J Dermatol, 129, 39-41.)	1993	24 PUVA skin cancer cases and 96 PUVA controls	Evaluated co-carcinogens with PUVA and found coal tar was not a risk factor	Coal tar did not increase risk of skin cancer even though its use was high.
Bhate et al. (Bhate SM, Sharpe GR, Marks JM, Shuster S, Ross WM, 1993, Prevalence of Skin And Other Cancers in Patients With Psoriasis, Clinical And Experimental Dermatology, 18, 401-4.)	1993	2,247 psoriasis patients receiving coal tar, psoralens, arsenic, methotrexate, and other therapies.	No increased risk seen due to coal tar treatment.	Coal tar was not found to increase the risk of skin cancer.

Summary of Epidemiological Studies and Review Articles on the Use of Coal Tar Containing Pharmaceuticals (5/5)

Author	Date	Study Population	Conclusion Of Report	Notes Regarding Coal Tar As A Risk Factor
Jemec & Østerlind (Jemec G.B.E. and A. Østerlind. 1994. Cancer in patients treated with coal tar: a long-term follow up study. *J Eur Acad Dermatol Venereol* 3:153-156.)	1994	88 patients treated extensively with coal tar from 1917-1937.	No increase in total cancers.	Coal tar was not found to increase the risk of cancer.
Van Schooten and Godschalk (Van Schooten, F, Godschalk, R. 1996. Coal Tar Therapy: Is it Carcinogenic? Drug Safety 15(6):374-377)	1996	No specific population addressed	No clearly increased skin cancer incidences have been reported in psoriasis patients who have been exposed to therapeutically high doses of coal tar.	Supports conclusion that coal tar does not increase risk of skin cancer because many patients can be presumed to have received coal tar treatment.
Hannuksela-Svahn et al. (Hannukesela-Svahn, A., E. Pukkala, E. Läärä, K. Poikolainen, and J. Karvonen. 2000. Psoriasis, its treatment, and cancer in a cohort of Finnish patients. *The Journal of Investigative Dermatology* 114(3):587-590)	2000	5,687 psoriasis patients receiving coal tar + UV treatment.	No increase in squamous cell carcinoma or non-Hodgkin's lymphoma above expected levels.	Coal tar was not found to increase the risk of skin cancer or non-Hodgkin's lymphoma.
Roelofzen et al. (Roelofzen, J., K. Aben, U. Oldenhof, P. Coenraads, H. Alkemade, P. van de Kerkhof, P. van der Valk, and L. Kiemeney. 2010. No increased risk of cancer after coal tar treatment in patients with psoriasis or eczema. *Journal of Investigative Dermatology* 130: 953.)	2010	13,200 patients with psoriasis and eczema. 8,062 received coal tar treatments.	No increase in skin cancer or cancer at other sites above expected levels.	Coal tar was not found to increase the risk of cancer.

Summary of EPA Epidemiology in Hazard Identification for Skin Cancer

- No statistically significant epidemiological studies
- Many negative epidemiological studies
- Many are “not epidemiology”: Old case reports that have little or no relevance because doses were massive, exposure times were very high, and industrial and personal hygiene was nonexistent

Human Skin Graft Studies

- Five studies of human skin grafted to mice demonstrate that human skin behaves differently from mouse skin
  - Human skin grafts not susceptible to PAH-induced tumors
  - Mouse skin surrounding the human grafts develop tumors from PAH
  - Human skin grafts susceptible to UV-induced tumors
- EPA (2013) dismissed human skin xenograft studies arguing that skin grafts don't behave normally (based on 1 paper)
- Did not cite other papers that demonstrate the utility of human skin grafts

Human Skin Graft Papers with PAHs

- Urano et al. (1995) (BaP, DMBA)
- Atillasoy et al. (1997) (DMBA)
- Graem (1986) (DMBA)
- Soballe et al. (1996) (DMBA)
- Kurtz et al. (2004) (DMBA)

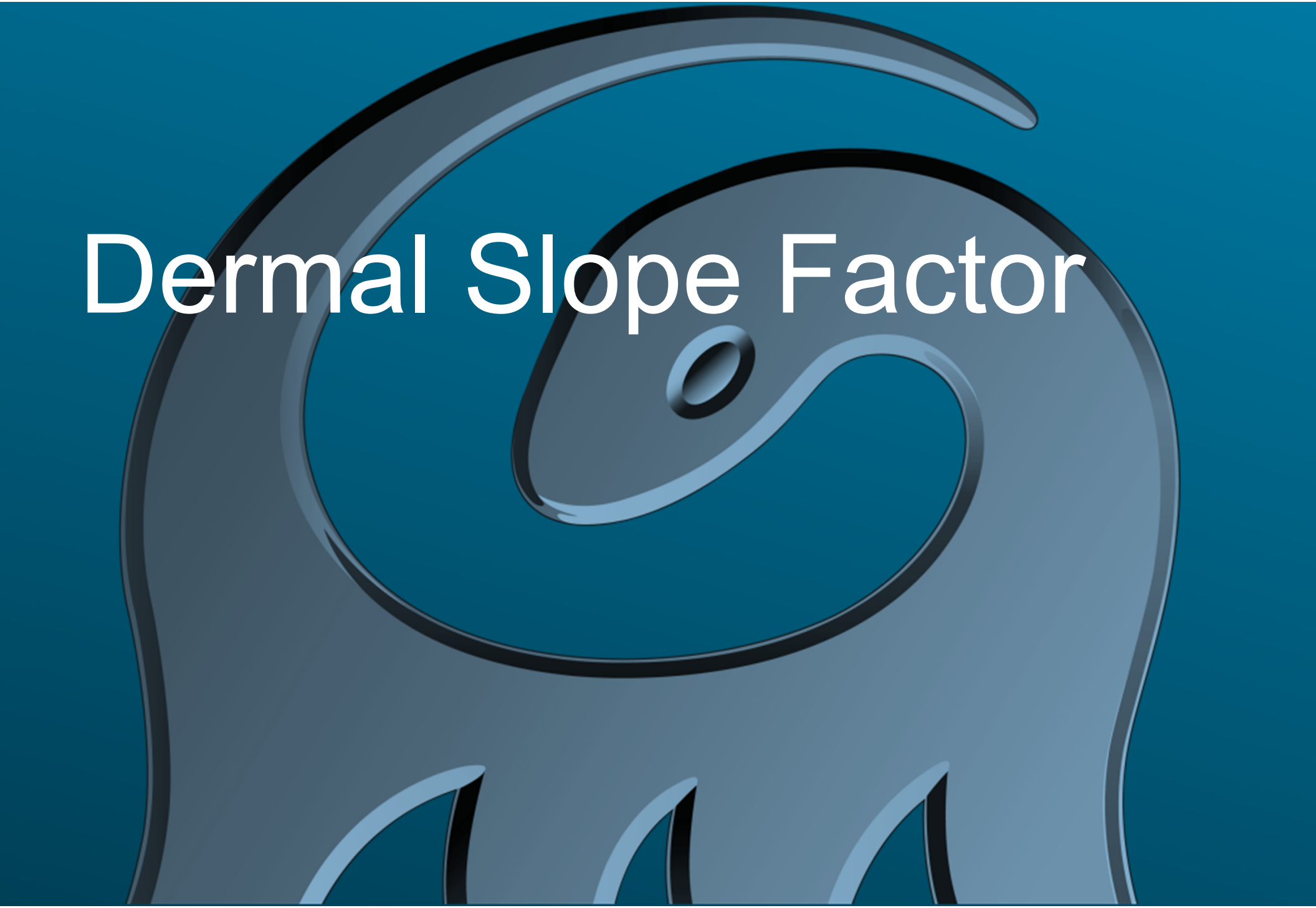
Viability of Human Skin Grafts

- Athar and Kopelovich (2011)
- Hachiya et al. (2009)
- Richmond and Su (2008)
- Anna et al. (2007)
- Morton and Houghton (2007)
- Balmain and Harris (2000)
- Nomura et al. (1997)
- Kim et al. (1992)
- Zaidi et al. (1992)
- Das et al. (1986)
- Haftek et al. (1981)
- Reed and Manning (1973)

Conclusions on Skin Cancer

- Skin cancer from continuous, high level, long duration exposure to PAH mixtures is not a hazard in 2013
- Current chemical regulations should focus on current hazards, not historical hazards
- No human studies link BaP to skin cancer
- FDA: “Upon reviewing the published studies, the agency does not find that there is evidence to implicate the use of OTC coal tar containing drug products as an independent risk factor for the development of skin cancer.”

Dermal Slope Factor



Dermal Slope Factor (DSF)

- 9 studies identified as critical
- Several omitted
- 12 PODs and candidate DSFs derived from 9 studies
- 9 giving lower DSFs were rejected
- DSF based on results from 2 studies
- Poorest of all the studies
  - Sivak et al. (1997)
  - Poel (1959)

Depot/Reservoir Effect

- Poel (1959): “In our own experiments, fluorescence of the exposed skin has been observed to persist for more than a week after a single application of benzopyrene, and comparable fluorescent periods have been observed with the more potent agents, 9,10-dimethyl-1,2-benzanthracene (DMBA) and methyl cholanthrene (MCA), on mouse skin. Apparently, the ‘single exposures’ of past experiments were in effect exposures of extended duration.”

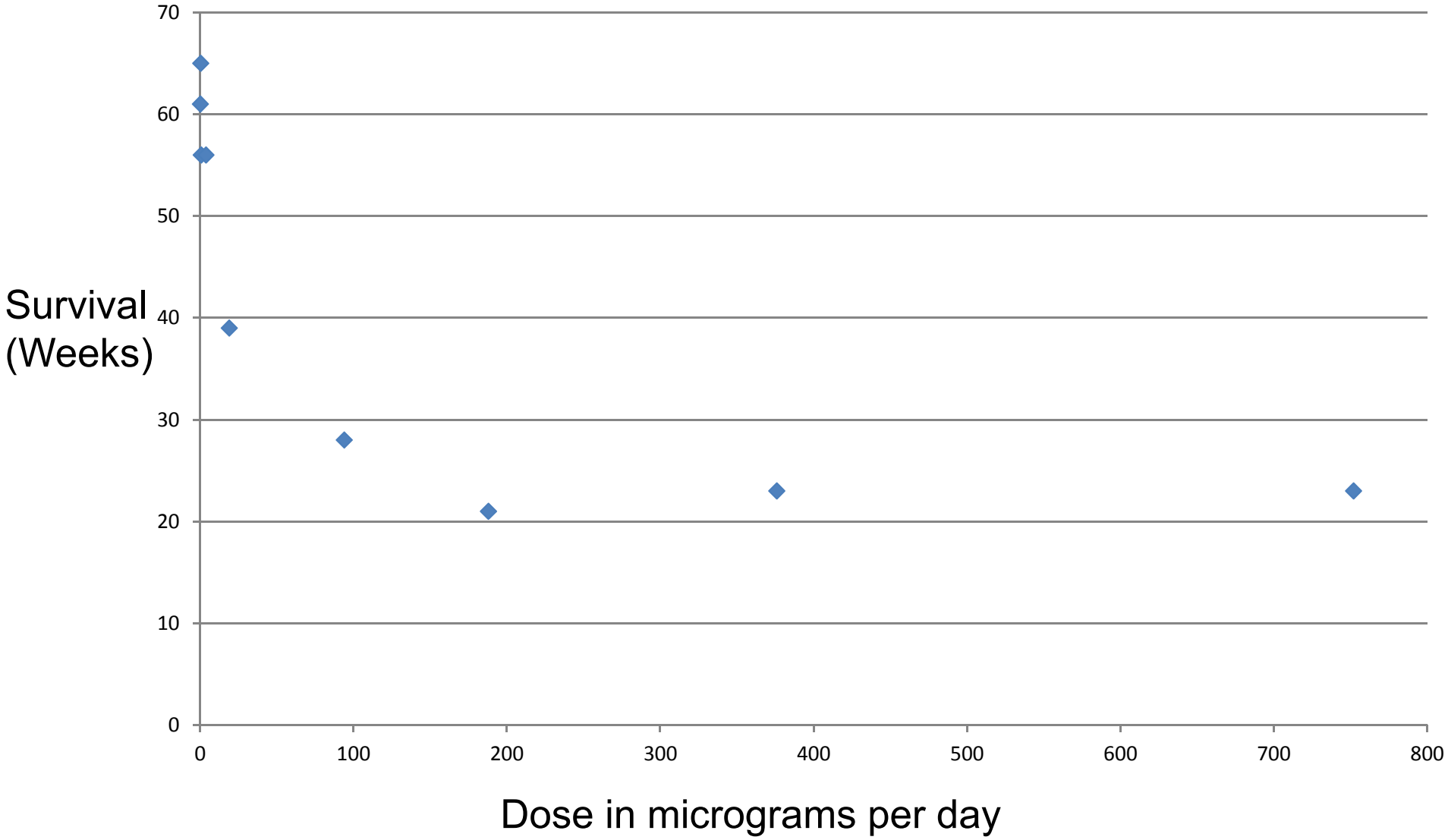
DSF Critical Review

- Dermal doses not amenable to traditional dose-response assessment
- Inadequate & poorly defined dosimetry
- Exceeded the maximally tolerated dose and failed to meet EPA criteria for dermal studies
- Doses were inappropriately averaged over weeks when mice were dead
- EPA's Benchmark Dose Modeling criterion for goodness of fit of data ignored (alpha = 0.05) and a less stringent criterion used (alpha = 0.10)
- Used linear extrapolation even with clear thresholds in mouse & human studies

Maximum Tolerated Dose Exceeded

- Skin lesions and high mortality
- Sivak et al. (1997): “With respect to skin lesions, Group 24, with the highest dose of BaP (0.01%) applied repeatedly, had an incidence of 80% of scabs and sores.”
  - Survival decreased from 90 weeks to 64 weeks in high dose group
- Poel (1959): Discusses skin lesions and states: “Carcinogenesis is an extreme form of reactive hyperplasia to a persistent, physiologically irreparable state of tissue damage…”
  - Survival decreased from 60 weeks to 23 weeks in the high dose group

Poel (1959) Mean Survival v. Dose



Attributes of Key Studies

Study Citation	BaP source or purity defined?	BaP concentration verified?	Delivered dose quantified?	Skin surface area specified?	Exceeds MTD?	Doses averaged over dead animals?
Sivak et al. (1997)	No	No	No (no details)	No	Noted	Yes
Poel (1959)	No	No	No (one drop)	No	Noted	Yes
Poel (1960)* (SWR)	No	No	No (one drop)	No	Likely	Not known
Poel (1960)* (C2HeB)	No	No	No (one drop)	No	Likely	Not known
Poel (1960)* (A/He)	No	No	No (one drop)	No	Likely	Not known
Roe et al. (1970)	Source identified	No	Yes (calibrated pipette)	No	Likely	No
Schmidt et al. (1973) (Swiss)	No	No	No (one drop)	No	Not likely	No
Schmidt et al. (1973) (NMRI)	No	No	No (one drop)	No	Not likely	No
Schmahl et al. (1977)	No	No	Possibly (syringe)	No	Not likely	No
Habs et al. (1980)	No	No	Yes (calibrated Hamilton syringe)	No	Likely	Yes
Habs et al. (1984)	Yes (>96% purity)	No	Yes (calibrated Hamilton syringe)	No	Likely	No
Grimmer et al. (1983)	No	No	No	No	Likely	No
Grimmer et al. (1984)	No	No	No	No	Likely	No

*Actually Poel (1963)

Summary of Reasons USEPA (2013) Used to Dismiss Certain Studies

Study Citation	USEPA (2013) Reasons for Dismissal	Actual Facts from the Cited Studies
Poel (1960)* (SWR mice)	No characterization of survival/exposure duration	Such information is not necessary. Average daily dose was provided. Animals were treated "until they died or a persistent skin tumor developed." Range and median time-to-tumor was reported for each dose group.
Poel (1960)* (C2HeB mice)	No characterization of survival/exposure duration	Such information is not necessary. Average daily dose was provided. Animals were treated "until they died or a persistent skin tumor developed." Range and median time-to-tumor was reported for each dose group.
Poel (1960)* (A/He mice)	Not listed at all	Not listed at all
Schmidt et al. (1973) (Swiss)	No characterization of exposure duration.	Such information is not necessary. Daily dose information was provided. Animals were treated until "spontaneous death of after sacrifice when neoplasms appeared."
Schmidt et al. (1973) (NMRI)	No characterization of exposure duration.	Such information is not necessary. Daily dose information was provided. Animals were treated until "spontaneous death of after sacrifice when neoplasms appeared."
Schmahl et al. (1977) (NMRI)	No characterization of exposure duration.	BaP was administered "until their natural death, unless they developed a carcinoma at the site of application, at which time they were killed." Average daily dose provided.

Summary of Reasons USEPA (2013) used to dismiss Certain Studies

Study Citation	USEPA (2013) Reasons for Dismissal	Actual Facts from the Cited Studies
Habs et al. (1980) (NMRI)	Higher overall exposure range; unclear overall duration of exposure	Exposure was for the animals' lifetime for all dose groups. Survival data shown for all dose groups.
Habs et al. (1984) (NMRI)	No characterization of exposure duration for high exposure; high response a lowest exposure limits usefulness of low-dose extrapolation.	Exposure reported as "for life" and survival time given for all dose groups (648 days for low dose and 528 days for high dose); low dose gave the lowest response.
Grimmer et al. (1983) (CFLP)	No characterization of exposure duration.	Exposure duration reported as 104 weeks.
Grimmer et al. (1984) (CFLP)	No characterization of exposure duration.	Exposure duration reported as 104 weeks.

Levin et al. (1977) and Nesnow et al. (1983) not considered at all.

DSF "Dose Adjustment"

- Cancer slope factors based on lifetime average daily dose
- Mice strains have differing normal lifespans
- Mice used in the actual PAH studies have average lifespan ~60-68 weeks
- DSF assumed that they should live 104 weeks
- DSF averaged the actual doses over an assumed 104 week lifespan (even though animals were dead after week 60!)
- Nonsensical "dose adjustment" drives slope factor up by 3X

Average Daily Dose (µg/day) During Animals' Lifetimes	EPA's Adjusted Dose (µg/day) Dose averaged over 104 weeks
0	0
0.06	0.05
0.16	0.16
0.32	0.24
1.6	0.80

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Sivak et al. (1997) Has a Threshold

Average Daily Dose (µg/day)	Tumor Incidence
0	0
0.01	0
0.14	17%
1.43	90%

Poel et al. (1963) Has Thresholds

Average Daily Dose (µg/day)	SWR Mice Tumor Incidence	A/He Mice Tumor Incidence	C3HeB Mice Tumor Incidence
0	0	0	0
0.06	0	0	0
0.16	9%	0	18%
0.32	83%	0	24%
1.63	71%	0	61%
8.14	100%	91%	100%

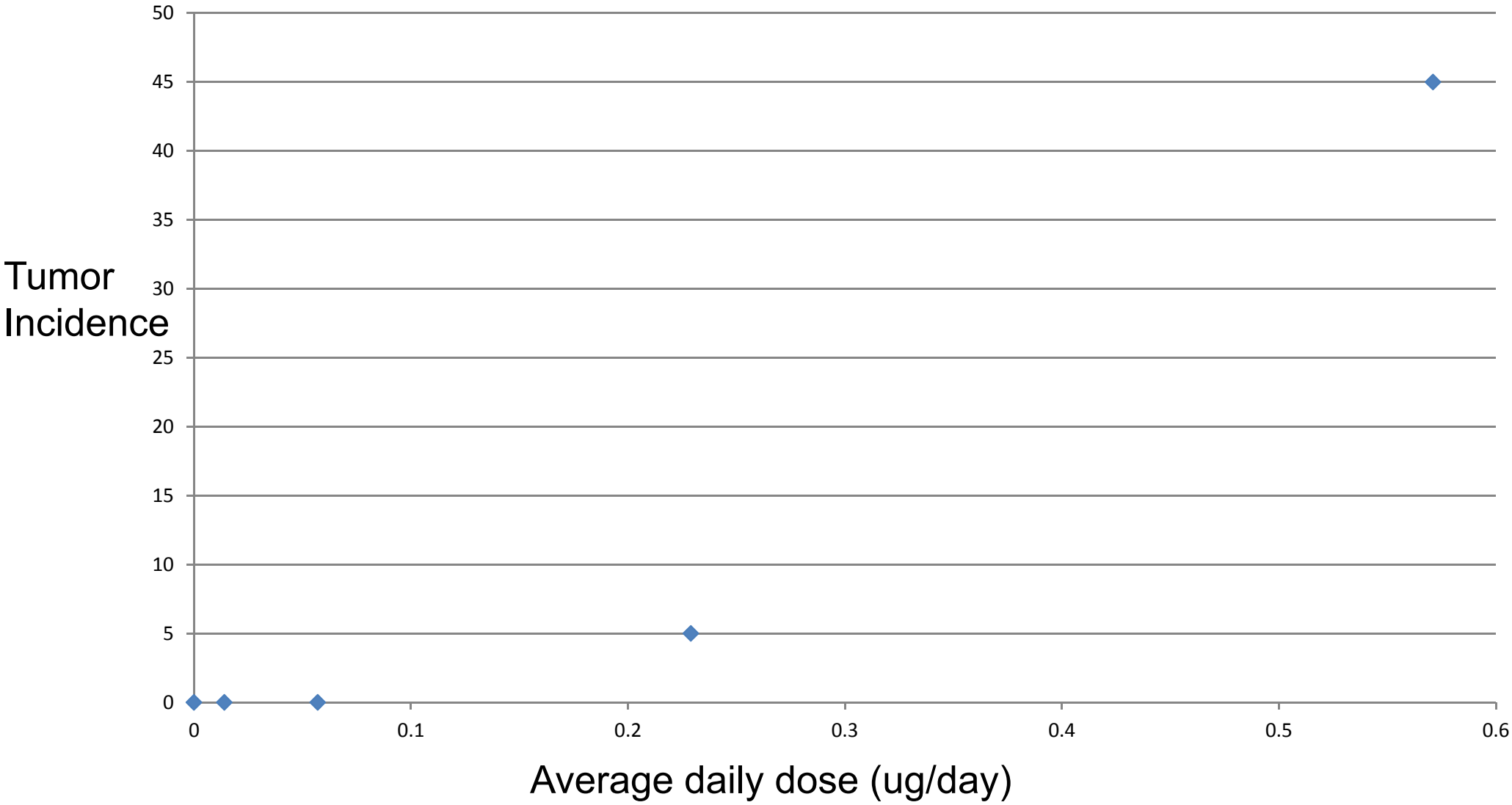
"For each strain, a threshold dose was apparent below which no tumors were induced despite lifelong repeated exposures. Threshold doses for tumor development are thus demonstrable, as determined by the biologic background of the exposed animal, and not merely by an absolute amount of carcinogen."

Schmidt et al. (1973) Has Thresholds

Average Daily Dose (µg/day	Swiss Mice Tumor Incidence	NMRI Tumor Incidence
0	0	0
0.01	0	0
0.06	0	0
0.23	5%	2%
0.57	45%	30%

Schmidt, et al. 1973. Investigations of the carcinogenic burden by air pollution in man, VI. Experimental investigations to determine a dose-response relationship and to estimate a threshold dose of benzo(a)pyrene in the skin of two different mouse strains. Zentralbl Bakteriol, Parasitenkd, Infektionskrankh Hyg, Abt 1: Orig, Reihe B 158: 62-68.

Schmidt et al. (1973) Threshold



Summary of USEPA $BMDL_{10}$ Values from USEPA (2013) and from *de novo* Benchmark Dose Modeling

Study	USEPA $BMDL_{10}$ (µg/day) Table 2-11	USEPA $BMDL_{10}$ (µg/day) TableE-23	Actual $BMDL_{10}$ (total tumors) (µg/day)
Poel (1959)	0.078*	0.078*	0.216
Sivak et al. (1997)	0.058*	0.058*	0.076
Poel (1960) (SWR)	0.11	Not listed	0.13
Poel (1960) (C2HeB)	0.11	Not listed	0.11
Poel (1960) (A/He)	Not presented	Not listed	1.96
Roe et al. (1970)	0.39	0.48	0.73 0.92 (highest dose removed)
Schmidt et al. (1970) (Swiss)	0.22	0.22	0.22
Schmidt et al. (1970) (NMRI)	0.29	0.29	0.33
Schmahl et al. (1977)	0.15	0.15	0.24
Habs et al. (1980)	0.24 0.44	0.215	0.24
Habs et al. (1984)	0.056 0.37	0.056	0.068
Grimmer et al. (1983)	0.21 1.0	0.21	0.25
Grimmer et al. (1984)**	0.48 Based on MDML of 70%	0.48 Based on MDML of 70%	Data unsuitable for modeling
Cavalieri et al. (1983)	Not done	Not done	0.22
Levin et al. (1977)	Not done	Not done	0.34
Nesnow et al. (1983) Males	Not done	Not done	1.32
Nesnow et al. (1983) Females	Not done	Not done	1.54

* Values averaged for USEPA's proposed DSF
** Actually Grimmer et al. (1985)

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Dermal Slope Factor Should Not be Derived from Mouse Skin Studies

- Greater skin permeation of BaP in mouse skin
- Lesser DNA repair activity in mouse skin
- Greater promotional mechanisms in mouse skin
- Greater sensitivity of mouse skin to chemically induced tumorigenesis versus human skin
- Different mode of action of mouse skin tumorigenesis and human skin tumorigenesis
- Complex dosimetry which takes into account the fact that 2 or 3 times/week doses to the mouse skin do not clear and instead form an ever increasing skin depot dose

Summary of Appropriate PODs and Candidate DSFs from USEPA's Benchmark Dose Modeling Software

Reference	Mouse Strain	Selected Model[a]	BMR	POD_M= BMDL (µg/d)	Unadjusted Candidate Dermal Slope Factors[b] $(µg/d)^{-1}$	POD_{HED} (µg/d)	Adjusted Candidate Dermal Slope Factors[c] $(µg/d)^{-1}$
Male mice							
Poel (1960)[a,d]	SWR	LogProbit	10%	0.13	0.77	38.9	0.003
Poel (1960)[a,d]	C3HeB	Multiple Fits	10%	0.11	0.91	32.9	0.003
Poel (1960)[a,d]	A/He	Multiple Fits	10%	1.96	0.05	586.2	0.0002
Nesnow et al. (1983)	SENCAR	LogLogistic	10%	1.32	0.08	394.8	0.0003
Female mice							
Roe et al. (1970)	Swiss	LogProbit	10%	0.92	0.11	275.1	0.0004
Schmidt et al. (1973)	Swiss	LogProbit	10%	0.22	0.45	65.8	0.002
Schmidt et al. (1973)	NMRI	Multiple Fits	10%	0.33	0.30	98.7	0.001
Schmähl et al. (1973)	NMRI	LogProbit	10%	0.24	0.42	71.8	0.001
Habs et al. (1980)	NMRI	Multiple Fits	10%	0.24	0.42	71.8	0.001
Habs et al. (1984)	NMRI	Multiple Fits	10%	0.068	1.47	20.3	0.005
Grimmer et al. (1983)	CFLP	Multiple Fits	10%	0.25	0.40	74.8	0.001
Cavalieri et al. (1983)	Swiss	Multistage Cancer 2	10%	0.22	0.45	65.8	0.002
Levin et al. (1977)	C57BL/6J	LogLogistic	10%	0.34	0.29	101.7	0.001
Nesnow et al. (1983)	SENCAR	Weibull	10%	1.54	0.06	460.6	0.0002
			Geometric Mean	0.34	0.29	101.76	0.001
			Arithmetic Mean	0.56	0.44	168.50	0.001

[a] See Appendix E for modeling details.
[b] Unadjusted for interspecies differences. Slope factor=R/BMDLR, where R is the BMR expressed as a fraction.
[c] Adjusted for interspecies differences. Cross-species adjustment of dermal doses is based on allometric scaling using the ¾ power of body weight. POD_{HED} (µg/day) = POD_M (µg/day) × $(BW_H / BW_M)^{3/4}$.
[d] High exposure groups omitted prior to dose-response modeling.

Lack of Real World Validation

- Dermal slope factor cannot possibly be true
- Proposed DSF would be >100X higher than the OSF
- PAH risk assessments would be dominated by dermal exposures
- Ingesting PAHs would be inconsequential
- Soil RSLs would be below background everywhere
- Soil RSLs would be lower than typical levels of PAHs in food
- A major fraction of human skin cancer would be attributable to PAH exposures

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DSF Recommendations

- Withdraw DSF
- If not –
- Recalculate dosimetry using actual doses considering the “depot” effect
- Do not average the average daily doses for dead animals
- Include excluded studies
- Use proper goodness of fit criterion for BMDM
- Use entire scientific weight of evidence
- Do not use linear low dose extrapolation

Lung Cancer Hazard Identification

Lung Cancer Hazard Identification

- No persuasive information presented linking BaP to lung cancer
- Tier 1 studies:
  - One not significant
  - One significant
  - One should be rejected (Xu et al. 1996)
- Tier 2 studies:
  - Four significant
  - Four not significant
  - One did no significance testing
- IARC reports:
  - 13 significant
  - 25 not significant or negative
- None demonstrate role of BaP

Lung Cancer Hazard Identification

- Tier 1 studies are not “studies of benzo(a)pyrene” as stated
- Armstrong & Gibbs (2009) “…the shape of the exposure-response function and the mode of combination of risks due to occupational PAH and smoking remains uncertain.”
- Spinelli et al. (2006) did not show statistically significant increases in cancer incidence or mortality in the 6,423 workers. Significant only at >80 $\mu g/m^3$-years. Actual dose was higher.
- Xu et al. (1996) has methodological flaws and should be rejected.

Summary of Tier 1 Reports Cited by USEPA (2013) Alleging Human Lung Cancer

Citation	Worker Group	Studied Effect Reported by USEPA (2013)	Statistical Significance Reported by USEPA (2013)	Actual Reported Statistical Significance
Armstrong and Gibbs (2009)	Aluminum workers	1. Increase in lung cancer 2. Lung cancer increased with increasing BaP exposure levels	1. Significant 2. Significant	1. Significant 2. Significant
Spinelli et al. (2006)	Aluminum workers	1. Increase in lung cancer 2. Lung cancer increased with increasing BaP exposure levels	1. Significant 2. Significant	1. Not significant 2. No association with BaP possible, because only particulate BaP measurements were made
Xu et al. (1996)	Iron and steel workers	1. Increase in lung cancer 2. Lung cancer increased with increasing BaP exposure levels	1. Significant 2. Significant	1. Significant, but unexplained manner of calculating odds ratios makes all claims suspect 2. No association with BaP possible, because no information provided about collection and analysis of BaP samples

Summary of Tier 2 Reports Cited by USEPA (2013) Alleging Human Lung Cancer

Citation	Worker Group	Studied Effect Alleged by USEPA (2013)	Statistical Significance Reported by USEPA (2013)	Actual Reported Statistical Significance
Friesen et al. (2009)	Aluminum workers	1. Increase in lung cancer 2. Lung cancer increased with increasing BaP exposure levels	1. Not Significant 2.Not Significant	1. Not Significant 2. Not Significant. BaP exposures estimated from job exposure matrix and BaP measurements using unreported methods.
Olsson et al. (2010)	Asphalt workers	1. Increase in lung cancer 2. Lung cancer increased with increasing BaP exposure levels	1.One significant & 3 nonsignificant results 2. One nonsignificant trend with coal tar	1. One significant & 39 nonsignificant results 2. Nine nonsignificant trends. BaP not measured or estimated. PAH levels estimated from external database.
Costantino et al. (1995)	Coke oven workers	1. Increase in lung cancer 2. Lung cancer increased with increasing BaP exposure levels	1. Significant 2. Significant	1. Significant 2. No association with BaP possible, because only Coal Tar Pitch Volatiles measured.

Summary of Tier 2 Reports Cited by USEPA (2013) Alleging Human Lung Cancer (cont.)

Citation	Worker Group	Studied Effect Alleged by USEPA (2013)	Statistical Significance Reported by USEPA (2013)	Actual Reported Statistical Significance
Liu et al (1997)	Carbon electrode manufacture	1. Increase in lung cancer 2. Lung cancer increased with increasing BaP exposure levels	1. Significant 2. Significant	1. Significant 2. No trend data was presented; BaP data presented by USEPA is from one plant & onetime point and not associated with the SMR data.
Berger and Manz (1992)	Coke oven workers	1. Increase in lung cancer 2. Lung cancer increased with increasing BaP exposure levels	1. Significant 2. No trend information presented	1. Significant 2. No trend information presented; BaP measured 10 years earlier but not used in study.
Hansen (1989, 1991)	Asphalt workers	1. Increase in lung cancer 2. Lung cancer increased with increasing BaP exposure levels	1. Significant 2. No trend information presented	1. Significant 2. No trend information presented
Gustavsson & Reuterwall (1990)	Coke oven workers	1. Increase in lung cancer 2. Lung cancer increased with increasing BaP exposure levels	1. Not Significant 2. No trend information presented	1. Not Significant 2. No trend information presented
Moulin et al. (1989)	Carbon electrode workers	1. Increase in lung cancer 2. Lung cancer increased with increasing BaP exposure levels	1. Not Significant 2. No trend information presented	1. Not Significant 2. No trend information presented; No historical BaP information was available.
Hammond et al. (1976)	Paving workers	1. Increase in lung cancer 2. Lung cancer increased with increasing BaP exposure levels	1. Significant 2. No trend information presented	1. No significance testing performed 2. No trend information presented

Comparison of Information Reported in IARC Monographs to Results of the Cited Studies (1/6)

Worker Group	IARC Reported Results for Lung Cancer	Actual Results for Lung Cancer
Aluminum Production		
Gibbs et al. (2007), Gibbs and Sevigny (2007a), Armstrong and Gibbs (2009)	Significant	Significant
Bjor et al. (2008)	Significant but no trend with PAH exposure levels	Significant but no trend with PAH exposure levels
Spinelli et al. (2006), Friesen et al. (2007)	Not significant, but significant trend with estimated BaP exposure	Not significant; association with BaP exposure is not possible because only particulate BaP was measured; only highest estimated BaP group statistically significant.
Friesen et al. (2009); Sim et al. (2009)	Not significant	Not significant
Mur et al. (1987)	Not significant	Not significant
Moulin et al. (2000)	Not significant	Not significant
Romundstad et al. (2000)	Not significant	Not significant
Rockett and Arena (1983)	Not significant	Not significant
Gibbs and Sevigny (2007b)	Not cited in text	Not significant for those first hired 1960-69 or 1970-79 Significant for those first hired from 1950-59
Giovanazzi & D"Andrea (1981)	Not cited in text	Not significant
Carta et al. (2004)	Not cited in text	Not significant

Comparison of Information Reported in IARC Monographs to Results of the Cited Studies (2/6)

Worker Group	IARC Reported Results for Lung Cancer	Actual Results for Lung Cancer
Carbon electrode manufacture		
Teta et al. (1987)	Not significant	Not significant
Moulin et al. (1989)	Not significant	Not significant
Gustavsson et al. (1995)	Not significant	Not significant
Liu et al. (1997)	Significant , but "…it is questionable how much of the excess risk may be attributed to exposures in carbon electrode manufacture."	Significant, but the group included an unknown number of aluminum smelter workers
Donato et al. (2000)	Not significant	Not significant
Mori (2002)	Significant	Significant
Merlo et al. (2004)	Not significant	Not significant

Comparison of Information Reported in IARC Monographs to Results of the Cited Studies (3/6)

Worker Group	IARC Reported Results for Lung Cancer	Actual Results for Lung Cancer
Coal Gasification		
Doll et al. (1972)	Significant	Relative risk and significance level not provided
Berger & Manz (1992)	Significant	Significant
Martin et al. (2000)	Significant	Significant for highest exposure group but not significant for other exposure groups.
Kennaway & Kennaway (1947)	Significant	Significance level not provided
Kawai et al. (1967)	Significant, but "Precision in the estimation of expected numbers was low."	Paper must be disregarded. Expected number of lung cancer deaths in 1,451 person-years of observation was reported as 0.135 deaths.
Hansen et al. (1986)	Significant	Significant based on 7 cases in gasworkers compared to 6 in the controls.
Wu (1988)	Significant but IARC cannot evaluate the validity of the study.	Significant but the validity of the study cannot be validated.

Comparison of Information Reported in IARC Monographs to Results of the Cited Studies (4/6)

Worker Group	IARC Reported Results for Lung Cancer	Actual Results for Lung Cancer
Coal tar pitch (paving and roofing):		
Kennaway & Kennaway (1947)	Significance not discussed. Presented as increased risk.	Significance level not provided and category included workers besides pavers.
Kennaway & Kennaway (1951)	Significance not discussed. Presented as increased risk.	Mis-citation. No information on roofers, pavers, or any occupational groups.
Hammond, et al. (1976)	Significance not discussed. Presented as increased risk.	Significance level not provided.
Milham (1982)	Significance not discussed. Presented as increased risk.	Significance not discussed in Milham (1982)
Pukkala (1995)	Significance not discussed. Presented as increased risk.	Significant
Swaen & Slangen (1997)	Significance not discussed. Presented as increased risk.	Not significant
Stern et al. (2000)	Significance not discussed. Presented as increased risk.	Significant
Schoenberg et al. (1987)	Not significant	Not significant
Zahm et al. (1989)	Not significant	Not significant
Morabia et al. (1992)	Not significant	Not significant
Partanen & Boffetta (1994)	Significant meta-analysis for roofers	Significant meta-analysis for roofers, but not pavers
Bergdahl & Jarvholn (2003)	Not significant	Not significant
Randem et al. (2003)	Not significant	Significant but risk was greater in those with less time working.
Stucker et al. (2003)	Not significant	Not significant
Kauppinen et al. (2003)	Significant	Study should be excluded because 85% of the cohort had no exposure to coal tar pitch.

Comparison of Information Reported in IARC Monographs to Results of the Cited Studies (5/6)

Worker Group	IARC Reported Results for Lung Cancer	Actual Results for Lung Cancer
Coke production		
Costantino et al. (1995)	Significant	Significant
Wu (1988)	Significant	Significant, but IARC (2012) states that the methods were "insufficient."
Chau et al. (1993)	Significant	Significant for "near coke oven" workers but not for "coke oven" workers
Franco et al. (1993)	Significant	
Sakabe et al. (1975)	Not significant	Not significant
Swaen et al. (1991)	Not significant	Not significant
Buck & Reid (1956)	Significant	Not significant
Davies (1977)	Not significant	Not significant
Hurley et al. (1983)	Not significant	Not significant
Wu-Williams et al. (1993)	Not reported	Not significant

Comparison of Information Reported in IARC Monographs to Results of the Cited Studies (6/6)

Worker Group	IARC Reported Results for Lung Cancer	Actual Results for Lung Cancer
Soot (chimney sweeping)		
Evanoff et al. (1993)	Significant	Significant for 1950's -1980's Not significant for 1980's
Pukkala (1995)	Significant	Not significant
Pukkala et al. (2009)	Significant	Significant
Kennaway & Kennaway (1947)	No increase	No increase
Haldorsen et al. (2004)	Not significant	Not significant

Summary of Lung Cancer Epidemiology

- Workers in aluminum production, carbon electrode manufacture, coal gasification, paving & roofing, coke production and chimney sweeping have been studied
- Some studies have shown increases in cancer & some have not
- All workers were exposed to complex mixtures and the role of BaP, if any, cannot be determined

Inhalation Unit Risk

Inhalation Unit Risk (IUR)

- Thyssen et al. (1981) critical study
- Syrian Golden hamsters
- BaP on a salt aerosol
- Dose variable between animals in each group
- Little data in publication
- Obtained raw data from authors in 1990
- IUR based on tumors of larynx or pharynx

IUR Critical Review

- Pauluhn et al. (1985) not cited
- Contradictory study in same lab under same conditions
- Uncertainty & confusion - different numbers of animals and tumors cited in different places
- Dose variability exceeds international criteria for acceptability
- Animals with tumors received higher doses than the group average doses modeled
- Data show threshold, but IUR derived by linear low dose extrapolation

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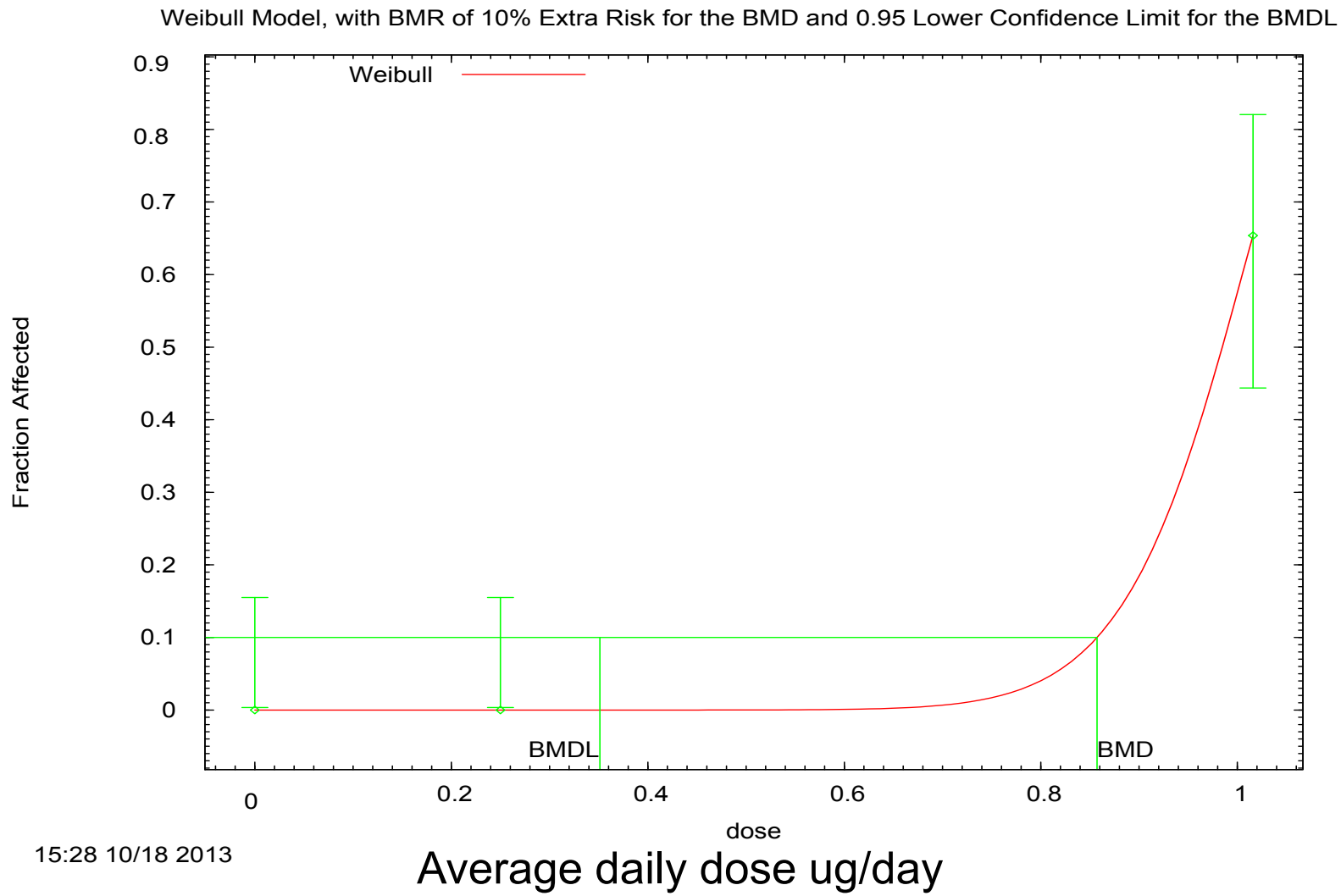
Thyssen et al. (1981) Threshold

Nominal Delivered Dose (mg/m^3)	Average Continuous Daily Dose (mg/m^3)	Tumor Incidence
0	0	0
2.2	0.25	0
9.5	1.02	65%
46.5	4.29	53%

Threshold for Thyssen et al. (1981)

Tumor incidence



Average daily dose ug/day

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Exceeds Maximally Tolerated Dose

- Particle overload exceeds maximally tolerated dose (MTD)
- NTP (1993): particle overload occurs at 6 mg/m^3 or lower
- Thyssen et al. (1981) doses above the threshold dose (9.5 & 46.5 mg/m^3) exceeded MTD
- EPA (2005): “In the case of inhalation studies with respirable particles, evidence of impairment of normal clearance of particles from the lung should be considered along with other signs of toxicity to the respiratory airways to determine whether the high exposure concentration has been appropriately selected (USEPA, 2001a).”

Thyssen Doses Massive

- Thyssen et al. (1981) - 47 mg/m^3
- Typical levels of BaP in smokers' houses - 0.000001 mg/m^3

Tumor Bearing Animals Had Higher Doses than the Group Average

- EPA (2013): "…weekly averages of chamber concentration measurements varied two- to fivefold from the overall average for each group, which exceeds the limit for exposure variability of <20% for aerosols recommended by OECD (2009)."
- 88% of tumor bearing animals in middle dose group - average doses higher than the modeled dose (group mean)
- 79% of tumor bearing animals in the high dose group - average doses higher than the modeled dose (group mean)

No Dose-Response

- Highest dose gives lower response than middle dose
- Benchmark dose modeling gives no fit unless highest dose is removed

BMDM Predicts BMDL That Exceeds NOAEL

- $BMDL_{10}$ not consistent with actual data
- IUR based on $BMDL_{10}$ of 0.20 mg/m^3
- Actual tumor response at 0.25 mg/m^3 is 0% incidence, not 10% incidence

IUR Recommendations

- Withdraw IUR
- If not –
- Clear up uncertainties in numbers of animals and tumors
- Re-model with average dose of animals developing tumors
- Obtain raw data from contradictory 1985 study and take into consideration
- Take into account 0% tumors in low dose group and derive IUR with non linear model

Inhalation Reference Concentration

Reference Concentration

- 2 studies identified as critical studies
- 1 dismissed because of single dose
- Point of Departure defined from Archibong et al. (2002) based on one endpoint of several studied
- Contradictory study of Wu et al. (2003) from the same laboratory dismissed

Contradictory Studies, Same Laboratory, Same Experimental System

- Archibong, Inyang, Ramesh, Greenwood, Nayyar, Kopsombut, Hood & Nyanda (2002)
  - 25 (µg/m^3) LOAEL for pup survival
  - No NOAEL defined
- Wu, Ramesh, Nayyar, & Hood (2003)
  - 75 (µg/m^3) LOAEL for pup survival
  - 25 (µg/m^3) NOAEL
- RfC estimates a NOAEL as 25/10 = 2.5 (µg/m^3)
- Wu et al. (2003) reports 25 (µg/m^3)
- Neutral approach: average them

RfC Recommendations

- Derive RfC from Wu et al. (2003) without database uncertainty factor
- If not –
- Derive candidate RfCs from four endpoints in Archibong et al. (2002) and Wu et al. (2003) without database uncertainty factor
- Use average of candidate RfDs

Oral Slope Factor

Oral Slope Factor (OSF)

- 2 studies identified as critical studies
- 10 candidate OSFs derived
- Proposed OSF: highest one

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Oral Slope Factor

Endpoint	Study	Candidate OSF (mg/kg-day) $^{-1}$
Alimentary tract (forestomach +)	Beland and Culp (1998)	1
Alimentary tract (forestomach +)	Kroese et al. (2001) (males)	0.4
Liver	Kroese et al. (2001) (males)	0.2
Intestines	Kroese et al. (2001) (males)	0.04
Kidney	Kroese et al. (2001) (males)	0.04
Skin, mammary	Kroese et al. (2001) (males)	0.04 – 0.06
Alimentary tract (forestomach +)	Kroese et al. (2001) (females)	0.3
Liver	Kroese et al. (2001) (females)	0.2
Intestines	Kroese et al. (2001) (females)	0.05

OSF Critical Review

- 2 chosen studies superior to old studies on which current OSF is based
- Did not use weight of evidence and focused on worst OSF
- OSF is dominated by forestomach
- Humans have no forestomach
- Forestomach used by EPA as surrogate to esophagus instead of using actual esophagus data
- Esophagus, tongue and larynx responses have thresholds

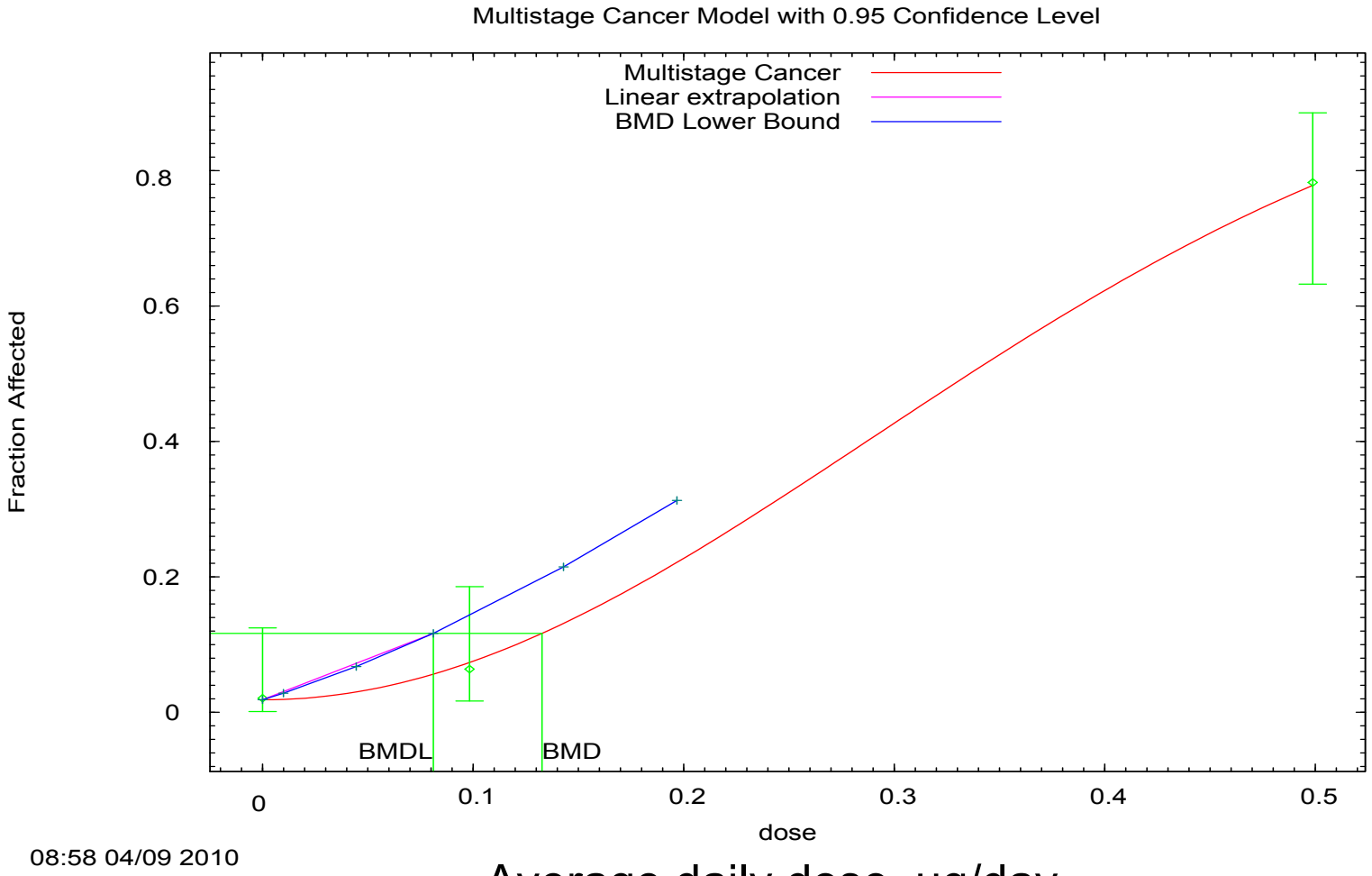
Beland & Culp (1998) Threshold for Esophagus Tumors

BaP in diet (ppm)	Incidence of Esophageal Tumors
0	0%
5	0%
25	4%
100	59%

Tongue and larynx cancer also has a threshold.

Nonlinearity in Dose-Response for Forestomach Tumors

Tumor Incidence



Average daily dose, ug/day

OSF Recommendations

- Use esophageal tumor data since humans have this organ & forestomach has been used in the past as a surrogate for esophagus
- OSF based on esophagus = 0.2 $(mg/kg\text{-}day)^{-1}$
- Use Beland and Culp esophagus OSF or average OSFs from both Beland and Culp and Kroese studies

Oral Reference Dose (RfD)

- 8 studies identified as critical studies
- Three endpoint categories
  - Developmental
  - Reproductive
  - Immunological
- Candidate RfDs derived
- EPA chose one of the most stringent

Oral RfD

Endpoint Category	Study	Candidate RfD (mg/kg-day)
Developmental	Chen et al. (2012)	0.0003
	Jules et al. (2012)	0.0002
Reproductive	Xu et al. (2010)	0.0004
	Zheng et al. (2010)	0.0002
	Mohamed et al. (2010)	Not calculated
	Gao et al. (2011)	0.00006
Immunological	Kroese et al. (2001)	0.002
	De Jong et al. (1999) (IgM)	0.002
	De Jong et al. (1999) (IgA)	0.005
	De Jong et al. (1999) (B cells)	0.005

RfD Critical Review

- Scientific weight of evidence bypassed
- Selective use of data & continuous focus on worst case
- Chen study did 77 tests
- RfD based on one test in one sex at one time point
- Elevated plus maze test measures anxiety in rats
- Results sensitive to housing, handling, maze construction, etc. No info provided to judge these factors.
- RfD based on finding that rats were *less* anxious. Is this adverse?

Tests Performed By Chen et al. (2012) (1/3)

Test Performed	Subtest Performed	Number of Observation Groups
Developmental Milestones		
Body weight		PND 5 PND 6 PND 7 PND 8 PND 9 PND 10 PND 11 PND 36 PND 71
Incisor eruption		Day observed
Eye opening		Day observed
Fur development		Day observed
Testis decent		Day observed
Vaginal opening		Day observed

Tests Performed By Chen et al. (2012) (2/3)

Test Performed	Subtest Performed	Number of Observation Groups
Neonatal Sensory and Motor Development Tests		
Surface righting reflex test (track 1 animals)		PND 12 PND 14 PND 16 PND 18
Negative geotaxis test (track 2 animals)		PND 12 PND 14 PND 16 PND 18
Cliff aversion test (track 1 animals)		PND 12
Forelimb grip strength test (track 2 animals)		PND 12
Open-field test	Horizontal Movement	PND 18 (track 1 animals) PND 20 (track 2 animals) PND 34 (track 3 animals) PND 69 (track 4 animals)
Open-field test	Vertical Movement, Rearing	PND 18 (track 1 animals) PND 20 (track 2 animals) PND 34 (track 3 animals) PND 69 (track 4 animals)
Elevated plus maze	Latency Time of the first entry into an open arm	Male PND 35 (track 3 animals) Male PND 70 (track 4 animals) Female PND 35 (track 3 animals) Female PND 70 (track 4 animals)
Elevated plus maze	Time Spent in the Open Arm	Male PND 35 (track 3 animals) Male PND 70 (track 4 animals) Female PND 35 (track 3 animals) Female PND 70 (track 4 animals)
Elevated plus maze	Number of Entries into the Open Arms	Male PND 35 (track 3 animals) Male PND 70 (track 4 animals) Female PND 35 (track 3 animals) Female PND 70 (track 4 animals)
Elevated plus maze	Number of Entries into the Closed Arms	Male PND 35 (track 3 animals) Male PND 70 (track 4 animals) Female PND 35 (track 3 animals) Female PND 70 (track 4 animals)

Tests Performed By Chen et al. (2012) (3/3)

Test Performed	Subtest Performed	Number of Observation Groups
Neonatal Sensory and Motor Development Tests		
Morris water maze	Escape Latency	Adolescent males PNP 36 (track 3 animals) PNP 37 (track 3 animals) PNP 38 (track 3 animals) PNP 39 (track 3 animals) Adolescent females PNP 36 (track 3 animals) PNP 37 (track 3 animals) PNP 38 (track 3 animals) PNP 39 (track 3 animals) Adult males PNP 71 (track 4 animals) PNP 72 (track 4 animals) PNP 73 (track 4 animals) PNP 74 (track 4 animals) Adult females PNP 71 (track 4 animals) PNP 72 (track 4 animals) PNP 73 (track 4 animals) PNP 74 (track 4 animals)
Morris water maze	Number of Times Animal Crossed Original Platform in Probe Test	Male PNP 40 (track 3 animals) Male PNP 75 (track 4 animals) Female PNP 40 (track 3 animals) Female PNP 75 (track 4 animals)
Morris water maze	Time Spent in the Target Quadrant	Male PNP 40 (track 3 animals) Male PNP 75 (track 4 animals) Female PNP 40 (track 3 animals) Female PNP 75 (track 4 animals)

Elevated Plus Maze

- Increased entries into open arm measures reduction in anxiety

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Significance of Elevated Plus Maze Effects in Chen et al. (2012)

Effect	Male PND 35	Male PND 70	Female PND 35	Female PND 70
Latency of 1st Entry, Open Arm	No significant effects	Medium dose significant	No significant effects	Medium dose significant
Open Arm Entries	No significant effects	High dose significant	No significant effects	Medium dose significant*
Time in Open Arms	No significant effects	Medium dose significant	High dose significant	Low dose significant
Closed Arm Entries	No significant effects	High dose significant	No significant effects	Medium dose significant

* Used for benchmark dose modeling

RfD Recommendations

- Derive multiple candidate RfDs from each study if relevant and use them all
- Reject Chen et al. (2010) due to insufficient reporting & arbitrary designation of *adverse*
- Do not use a database uncertainty factor for BaP
- Average of candidate RfDs is 0.002 mg/kg-day

QUESTIONS?

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Imagine the result

Implications

Regional Screening Level	Existing	Proposed	Difference
Residential Soil RSL [a]	0.015 mg/kg (ca)	0.0035 mg/kg (ca)	4x lower
Industrial Soil RSL	0.21 mg/kg (ca)	0.031 mg/kg (ca)	7x lower
Residential Ambient Air RSL	0.00087 µg/m^3 (ca)	0.0019 µg/m^3 (ca)	2x higher
Industrial Ambient Air RSL	0.011 µg/m^3 (ca)	0.0088 µg/m^3 (nc)	2x lower
Tapwater RSL	0.0029 µg/L (ca)	0.022 µg/L (ca)	7x higher

