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National Institute of Environmental Health Sciences
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Dear Dr. Masten,

The following comments are submitted on behalf of the more than 2 million members and supporters of People for the Ethical Treatment of Animals (PETA) in response to the nominations of substances to NTP for study in 2008 (April 15, 2008; *Federal Register* 73(73):20289). PETA is committed to using the best available science to protect animals from suffering and to promote the acceptance of human-relevant methods for risk assessment.

Specific comments are submitted for 2-ethylhexyl p-methoxycinnamate and vanadium, tetravalent and pentavalent forms. NTP has recommended additional animal tests for these substances that would result in the poisoning and death of thousands of animals if carried out. In each case, we urge NTP to thoroughly consider potential human exposure, existing toxicity data and the application of non-animal test methods in order to avoid unnecessary and duplicative animal tests.

Thank you for your attention to these comments. I can be reached at (757) 622-7382, ext. 8001, or by e-mail at josephm@peta.org.

Sincerely,

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Vanadium, tetravalent and pentavalent forms

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2-Ethylhexyl p-methoxycinnamate

OCTYL METHOXYCINNAMATE

Ocytl methoxycinnamate (OMC), a common sunscreen ingredient, was nominated by the National Cancer Institute (NCI) for comprehensive toxicological characterization including carcinogenicity and developmental toxicity studies as well as characterization of photodecomposition products. This nomination is reportedly based on concerns over widespread consumer exposure and evidence of weak estrogenic and reproductive effects.

We strongly urge the NTP to consider the following points before subjecting thousands of animals to these unnecessary tests.

Update on the existence of in vitro and in vivo data on the toxic potential of OMC
Although the NCI summary indicates that OMC has repeatedly demonstrated weak estrogenic effects, current understanding of the endocrine disrupting potential of this compound is more extensive than indicated in the 2006 report. At least six additional short-term and chronic studies of the absorption and endocrine effects of OMC have since been published (Kunz and Fent, 2006; Seidlová-Wuttke et al, 2006; Janjua et al, 2007; Klammer et al, 2007; Janjua et al, 2008; Szwarcfarb et al, 2008). Pubmed and the National Library of Medicine's ToxNet database also list multiple studies relevant to the absorption (Treffel and Gabard, 1996; Potard et al, 1999; Walters and Roberts, 2002) and endocrine disruption capabilities (Schruers et al, 2002; Schmid et al, 2004; Heneweer et al, 2005; Kunz et al, 2006) of OMC that were not referenced in the NCI summary. In addition to potential endocrine effects, the NCI report summarizes preliminary studies looking at other aspects of OMC but does not include several studies addressing its toxicity (Xu and Parsons, 1999; Rachoń et al, 2006), and carcinogenicity (Trueman and Schupbach, 1983; Young et al, 1987; Reeve and Kerr, 1996).

The NCI summary touched upon the lack of concordance between the endocrine effects seen in animal studies and the limited human studies (Treffel and Gabard, 1996; Janjua et al, 2007; Janjua et al, 2008). It should be noted, however, that this lack of effects in humans and the consistently weak nature of the health effects in animals has been conservatively taken by many in the field as an indication that sunscreen ingredients like OMC are unlikely to pose a human health concern when used correctly (Gasparro et al, 1998; Nhynek and Schaefer, 2001; Lautenschlager et al, 2007). Unlike the NCI, which believes that extensive toxicological studies in animals are warranted to address the apparent discrepancies, these reviews give no suggestion that further animal studies would help to resolve issues of human safety.

In vitro methods can better predict toxicological/carcinogenic effects of OMC
Although the NCI is pushing for extensive animal studies of OMC, it is important to emphasize that *in vitro* methodologies have, and will continue to, provide much more informative data for human study design and risk assessment. Several standard *in vitro* tests for toxicity, genotoxicity, mutagenicity and carcinogenicity have been optimized for the detection of photomutagenicity/toxicity of topically applied compounds and UV filters (DiNardo et al, 1985; Dean et al, 1991; 1992; Chäetelat et al, 1993a; 1993b;

Henderson et al, 1994; Utesch and Spittgerber, 1996; Jones et al, 1999; Xu and Parsons, 1999; Flamand et al, 2006) making them more precise and powerful tools for sunscreen testing than animal models. In fact, several of the animal studies of OMC cited have used methods with questionable biological relevance. For example, the Schnieder et al. (2005) study referenced in the NCI report involved lifelong feeding of OMC to rats. Not only is this route of administration unlikely to be relevant to actual human exposure, but it also resulted in significant behavioral and physical effects, such as appetite loss and stomach ulceration, that undermine any interpretation of the hormonal and developmental endpoints.

OMC is an ideal candidate for human exposure and epidemiological studies

In addition to *in vitro* screening assays, epidemiological studies of human exposure to OMC can provide much more useful information for making human risk assessments than can extrapolation of animal results. With the degree of current and expected human exposure, including the occupational exposure associated with manufacturing the large quantities described in the NCI report (also Van Wijngaarden and Hertz-Picciotto, 2004), OMC is an ideal candidate for epidemiological analysis. Heneweer et al (2005) noted that despite the urgent need, there are currently no epidemiologic studies of the association between sunscreen use and adverse endocrine responses in humans.

Concerns over the association of sunscreen use and increased incidence of malignant melanoma have prompted multiple *in vitro* studies of reactive oxygen species (ROS) formed by UV filters (Knowland et al, 1993; Allen et al, 1996; McHugh and Knowland, 1997; Hanson et al, 2006) and several large-scale epidemiological studies (Graham et al, 1985; Beitner et al, 1990; Garland et al, 1992; Autier et al, 1995; Wolf et al, 1998; Weinstock, 1999; Vainio and Bianchini, 2000; Westerdahl et al, 2000; Bastuji-Garin and Diepgen, 2002; Marshall et al, 2003). This approach demonstrates the utility of international case-controlled epidemiological studies in assessing human risk from sunscreen ingredients, including OMC. As these epidemiological studies are expanded to address specific UV filters, filter combinations, different biomarkers and other cancers, they will effectively establish human health effects of OMC without the need for additional irrelevant animal studies.

What is meant by "characterization of photodegradation products" of OMC?

Although it is likely that "characterization of photodegradation products" in the context of the NCI nomination is referring to photostability of OMC, there is a possibility that it may be referring to additional toxicological studies of potential degradation products (such as ROS). It is difficult to comment on the necessity of these studies without a more specific definition, however, it should be noted that numerous studies have already examined the photostability and photodynamics of OMC (Selles et al, 1987; Marginean Lazar et al, 1997;Yener and Bayraktar-Alpmen, 1997; Sayer et al, 1999; Chatelain et al, 2001; Serpone et al, 2002; Dondi et al, 2006; Krishnan et al, 2006; Wakefield and Stott, 2006; Gaspar and Campos, 2007; Pangnakorn et al, 2007; Krishnan and Nordlund, 2008). Also, as indicated above, the impacts of UV filter induced ROS are primarily being investigated with *in vitro* methods (Knowland et al, 1993; Allen et al, 1996; McHugh and

Knowland, 1997; Hanson et al, 2006) and these studies would not be advanced by additional toxicological analysis in animals.

In summary, in nominating OMC to the NTP, NCI failed to convey the extent to which the toxicological properties of this compound have already been studied. NCI also failed to acknowledge the applicability of *in vitro* methods specifically designed to test topically applied UV filters and human epidemiological studies to risk assessment of OMC. These methods hold much more promise for resolving existing discrepancies between toxicological effects in animal and in human than simply repeating animal studies. We recommend that the NTP reject the extensive animal testing strategy proposed in this nomination and instead advocate appropriate *in vitro* assays, human clinical studies, and epidemiological analyses in the assessment of OMC.

Allen JM, Gossett CJ, Allen SK (1996) Photochemical formation of singlet molecular oxygen-10-2 in Aqueous solutions of several sunscreen active ingredients. Meeting of the American Society for Photobiology, Atlanta, Georgia, USA, June 15-20, 1996. *Photochem Photobio* 63 (special issue): 16S-17S.

Autier P, Dore J F, Schifflers E, et al (1995) Melanoma and use of sunscreens: An EORTC case control study in Germany, Belgium and France. *In. J Cancer* 61:749-755.

Bastuji-Garin S, Diepgen Tl (2002) Cutaneous malignant melanoma, sun exposure, and sunscreen use: epidemiological evidence. *British J Derm* 146 (1):24-30.

Beitner H, Norell SE, Ringborg U, Wennersten G, Mattson B (1990) Malignant melanoma: aetiological importance of individual pigmentation and sun exposure. *Br J Dermatol* 122 (1):43-51.

Chäetelat A, Albertini S, Dresp JH, Strobel R, Gocke E (1993) Photomutagenesis test development: I. 8-Methoxypsoralen, chlorpromazine and sunscreen compounds in bacterial and yeast assays. *Mutat Res* 292(3):241-50.

Chételat A, Dresp JH, Gocke E (1993) Photomutagenesis test development: II. 8-Methoxypsoralen, chlorpromazine and sunscreen compounds in chromosomal aberration assays using CHO cells. *Mutat Res* 292(3):251-8.

Chatelain E, Gabard B (2001) Photostabilization of butyl methoxydibenzoylmethane (Avobenzone) and ethylhexyl methoxycinnamate by bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb S), a new UV broadband filter. *Photochem Photobiol* 74(3): 401-06.

Dean SW, Lane M, Dunmore RH, Ruddock SP, Martin CN, Kirkland DJ, Loprieno N (1991) Development of assays for the detection of photomutagenicity of chemicals during exposure to UV light--I. Assay development. *Mutagenesis* 6(5):335-41.

Dean SW, Dunmore RH, Ruddock SP, Dean JC, Martin CN, Kirkland DJ (1992) Development of assays for the detection of photomutagenicity of chemicals during exposure to UV light. II. Results of testing three sunscreen ingredients. *Mutagenesis* 7(3):179-82.

DiNardo JC, Wolf BA, Morris WE, Tenebaum S, Schnetzinger RW (1985) Quantitative in vitro assay for the evaluation of phototoxic potential of topically applied materials. Part 2. Modification and assessment of low level activity. *J Soc Cosmet Chem* 36: 425-433.

Dondi D, Albini A, Serpone N (2006) Interactions between different solar UVB/UVA filters contained in commercial suncreams and consequent loss of UV protection. *Photochem Photobiol Sci* 5(9):835-43.

Flamand N, Marrot L, Belaidi JP, Bourouf L, Dourille E, Feltes M, Meunier JR (2006) Development of genotoxicity test procedures with Episkin, a reconstructed human skin model: towards new tools for in vitro risk assessment of dermally applied compounds? *Mutat Res* 606(1-2):39-51.

Garland C, Garland F, Gorham E (1992) Could sunscreens increase melanoma risk?. *Am J Public Health* 82 (4):614-5.

Gaspar LR, Campos PM (2007) Photostability and efficacy studies of topical formulations containing UV-filters combination and vitamins A, C and E. *Int J Pharm* 343(1-2):181-9.

Gasparro FP, Mitchnick M, Frank J (1998) A review of sunscreen safety and efficacy. *Photochem Photobiol* 68(3): 243-256.

Graham S, Marshall J, Haughey B, Stoll H, Zielezny M, Brasure J, West D (1985) An inquiry into the epidemiology of melanoma. *Am J Epidemiol* 122 (4):606-619.

Hanson Kerry M, Gratton E, Bardeen C (2006) Sunscreen enhancement of UV-induced reactive oxygen species in the skin. *Free Radical Biol Med* 41 (8): 1205-1212.

Henderson L, Fedyk J, Bourner C, Windebank S, Fletcher S, Lovell W (1994) Photomutagenicity assays in bacteria: factors affecting assay design and assessment of photomutagenic potential of para-aminobenzoic acid. *Mutagenesis*. 9(5):459-65.

Heneweer M, Muusse M, van den Berg M, Sanderson JT (2005) Additive estrogenic effects of mixtures of frequently used UV filters on pS2-gene transcription in MCF-7 cells. *Toxicol Appl Pharmacol* 208:170-7.

Janjua NR, Kongshoj B, Petersen JH, Wulf HC (2007) Sunscreens and thyroid function in humans after short-term whole-body topical application: a single-blinded study. *Br J Dermatol* 156(5):1080-2.

Janjua NR, Kongshoj B, Andersson AM, Wulf HC (2008) Sunscreens in human plasma and urine after repeated whole-body topical application. *J Eur Acad Dermatol Venereol* 22(4):456-61.

Jones PA, King AV, Lovell WW, Earl LK (1999) Phototoxicity testing using 3D-reconstructed human skin models. Annual Congress of the British Toxicological Society, Stoke on Trent, England, UK, April 18-21, 1999. *Human Exp Toxicol* 18(8): 537.

Klammer H, Schlecht C, Wuttke W, Schmutzler C, Gotthardt I, Köhrle J, Jarry H (2007) Effects of a 5-day treatment with the UV-filter octyl-methoxycinnamate (OMC) on the function of the hypothalamo-pituitary-thyroid function in rats. *Toxicology* 238(2):192-9.

Knowland J, McKenzie EA, McHugh PJ, Cridland NA (1993) Sunlight-Induced Mutagenicity of a Common Sunscreen Ingredient. *Febs Lett* 324(3): 309-13.

Krishnan R, Pradhan S, Timares L, Katiyar SK, Elmets CA, Nordlund TM (2006) Fluorescence of sunscreens adsorbed to dielectric nanospheres: parallels to optical behavior on hacat cells and skin. *Photochem Photobiol* 82(6):1557-65.

Krishnan R, Nordlund TM (2008) Fluorescence dynamics of three UV-B sunscreens. *J Fluoresc* 18(1):203-17.

Kunz PY, Fent K (2006) Multiple hormonal activities of UV filters and comparison of *in vivo* and *in vitro* estrogenic activity of ethyl-4-aminobenzoate in fish. *Aquat Toxicol* 79(4): 305-24.

Kunz PY, Galicia HF, Fent K (2006) Comparison of in vitro and in vivo estrogenic activity of UV filters in fish. *Toxicol Sci* 90(2):349-61.

Lautenschlager, Stephan; Wulf, Hans Christian; Pittelkow, Mark R. (2007). Photoprotection. *Lancet* 370: 528-37.

Ma R, Cotton B, Lichtensteiger W, Schlumpf M (2003) UV filters with antagonistic action at androgen receptors in the MDA-kb2 cell transcriptional-activation assay. *Toxicol Sci* 74(1):43-50.

Marshall S, Poole C, Waller AE (2003) Sunscreen use and malignant melanoma risk: the jury is still out. *Am J Public Health* 93 (1).

Marginean Lazar G, Fructus AE, Baillet A, Bocquet JL, Marty JP, et al (1997) Sunscreens' photochemical behavior: in vivo evaluation by the stripping method . *Int J Cosmet Sci* 19(2): 87-101.

McHugh PJ, Knowland J (1997) Characterization of DNA damage inflicted by free radicals from a mutagenic sunscreen ingredient and its location using an in vitro genetic reversion assay. *Photochem Photobiol* 66(2): 276-81.

Nohynek G J, Schaefer H (2001) Benefit and Risk of Organic Ultraviolet Filters. *Reg Toxicol Pharmacol* 33 (3): 285-299.

Pangnakorn P, Nonthabenjawan R, Ekgasit S, Thammacharoen C, Pattanaargson Wanichwecharungruang S (2007) Monitoring 2-ethylhexyl-4-methoxycinnamate photoisomerization on skin using attenuated total reflection fourier transform infrared spectroscopy. *Appl Spectrosc* 61(2):193-8.

Potard G, Laugel C, Baillet A, Schaefer H, Marty JP (1999) Quantitative HPLC analysis of sunscreens and caffeine during in vitro percutaneous penetration studies. *Int J Pharm* 189(2): 249-260.

Rachoń D, Rimoldi G, Wuttke W (2006) In vitro effects of benzophenone-2 and octyl-methoxycinnamate on the production of interferon-gamma and interleukin-10 by murine splenocytes. *Immunopharmacol Immunotoxicol* 28(3): 501-10.

Reeve VE, Kerr CA (1996) Comparative protection from photocarcinogenesis by two UVB-absorbers matched for SPF in hairless mice. Meeting of the American Society for Photobiology, Atlanta, Georgia, USA, June 15-20, 1996. *Photochem Photobiol* 63 (special issue): 17S-18S.

Sayre R, Dowdy JC, Gerwig AJ, Shields WJ (1999) Sensitized photolysis of the sunscreen Octyl-MethoxyCinnamate caused by excitation of another sunscreen, Avobenzone, in films of a sunscreen product. *Photochem Photobiology* 69: 58S-58S.

Schmid P, Durrer S, Conscience M, Maerkel K, Henseler M, Gruetter M, Herzog I, Reolon S, Ceccatelli R, Faass O, Stutz E, Jarry H, Wuttke W, Lichtensteiger W (2004) Endocrine activity and developmental toxicity of cosmetic UV filters--an update. *Toxicology* 205(1-2):113-22.

Schreurs RH, Lanser P, Seinen W, Van der Burg B (2002) Estrogenic activity of UV filters determined by an in vitro reporter gene assay and in vivo transgenic zebrafish assay. *Arch Toxicol* 76: 257–261.

Seidlová-Wuttke D, Christoffel J, Rimoldi G, Jarry H, Wuttke W (2006) Comparison of effects of estradiol with those of octylmethoxycinnamate and 4-methylbenzylidene camphor on fat tissue, lipids and pituitary hormones. *Toxicol Appl Pharma* 214(1):1-7.

Selles E, Aberturas MR, Fresno MJ (1987) Photostability of 2-ethylhexyl-p-methoxycinnamate in sunscreen milks**.** *An R Acad Farm* 53(1): 153-158.

Serpone N, Salinaro A, Emeline AV, Horikoshi S, Hidaka H, Zhao J (2002) An in vitro systematic spectroscopic examination of the photostabilities of a random set of commercial sunscreen lotions and their chemical UVB/UVA active agents. *Photochem Photobiol Sci* 1(12):970-81.

Szwarcfarb B, Carbone S, Reynoso R, Bollero G, Ponzo O, Moguilevsky J, Scacchi P (2008) Octyl-methoxycinnamate (OMC), an ultraviolet (UV) filter, alters LHRH and amino acid neurotransmitters release from hypothalamus of immature rats. *Exp Clin Endocrinol Diabetes* 116(2):94-8.

Treffel P, Gabard B (1996) Skin penetration and sun protection factor of ultraviolet filters from two vehicles. *Pharm Res* 13: 770-774.

Trueman RW, Schupbach M (1983) An assessment of the potential genotoxic activity of 4 sunscreen agents. *Mutat Res* 113: 310-311.

Utesch D, Splittgerber J (1996) Bacterial photomutagenicity testing: distinction between direct, enzyme-mediated and light-induced events. *Mutat Res* 361(1):41-8.

Vainio H, Bianchini F (2000) Cancer-preventive effects of sunscreens are uncertain. *Scandinavian J Work Environ Health* 26:529-31.

Van Wijngaarden E, Hertz-Picciotto I (2004) A simple approach to performing quantitative cancer risk assessment using published results from occupational epidemiological studies. *Science of the Total Environ* 332 (1-3): 81-87.

Wakefield G, Stott J (2006) Photostabilization of organic UV-absorbing and anti-oxidant cosmetic components in formulations containing micronized manganese-doped titanium oxide. *J Cosmet Sci* 57(5):385-95.

Walters KA, Roberts MS (2002) Percutaneous absorption of sunscreens. Book: Bronaugh, R. L.; Maibach, H.I. eds. *Topical absorption of dermatological products, New York: Dekker:* 465–481.

Weinstock MA (1999) Do sunscreens increase or decrease melanoma risk: An epidemiologic evaluation. *J Inv Derm Symp Proceed* 4:97-100.

Westerdahl J, Ingvar C, Masback A, Olsson H (2000) Sunscreen use and malignant melanoma. *In J Cancer.* 87:145-50.

Wolf P, Quehenberger F, Müllegger R, Stranz B, Kerl H (1998) Phenotypic markers, sunlight-related factors and sunscreen use in patients with cutaneous melanoma: an Austrian case-control study. *Melanoma Res.* 8 (4):370-378.

Xu C, Parsons PG (1999) Cell cycle delay, mitochondrial stress and uptake of hydrophobic cations induced by sunscreens in cultured human cells. *Photochem Photobiol* 69 (5): 611-616.

Yener G, Bayraktar-Alpmen G (1997) Photostability of 2-ethylhexyl-p-methoxycinnamate used in sunscreen preparations marketed in Turkey. *Acta Pharm Turc* 39(3): 111-114.

Young AR, Gibbs NK, Magnus IA (1987) Modification of 5-methoxypsoralen phototumorigenesis by UVB sunscreens: statistical and histologic study in the hairless albino mouse. *J Invest Dermatol* 89: 611-617.

VANADIUM COMPOUNDS

The National Institute of Environmental Health Sciences (NIEHS) nominated tetravalent and pentavalent vanadium for comprehensive toxicological characterization including chronic toxicity and carcinogenicity studies and multigeneration reproductive toxicity studies via the oral route of administration. The nomination is based on human exposure through drinking water and through use as a dietary supplement.

The weight of evidence clearly suggests that the toxicity of vanadium is low through oral exposure and that any adverse effects are likely to be mild and reversible. For example, the Expert Group on Vitamins and Minerals (EVM) of the U.K. Food Standards Agency observes that there have been very few reported cases of vanadium toxicity in humans where exposure has been by routes other than inhalation (EVM, 2002). Likewise, the Food and Nutrition Board of the National Academies' Institute of Medicine notes that there is no evidence of adverse effects associated with vanadium intake from food (the major source of exposure to vanadium for the general population) and that the risk of adverse effects resulting from excess intake of vanadium from food is very unlikely. Adverse effects reported from short-term and subchronic toxicity studies with human volunteers include abdominal pain, anorexia, nausea, and weight loss, which were reversible when treatment was reduced or ended (Institute of Medicine, 2001). This is partly explained by the fact that ingested vanadium is absorbed poorly – generally reported as less than 5% (EVM, 2002; Institute of Medicine, 2001). In fact, the NIEHS cites human data showing absorption to be 1% or less.

Typical oral exposures to vanadium are at levels well below what might reasonably cause concern. The Institute of Medicine established a tolerable upper intake level (UL) of 1.8 mg/day of elemental vanadium for adults based on a lowest observed adverse effects level (LOAEL) in rats of 7.7 mg/kg/day and an uncertainty factor of 300 (Institute of Medicine, 2001). Although the NIEHS cites a more recent publication by the European Food Safety Authority that declined to set a UL, the Institute of Medicine notes that the LOAEL upon which their UL is based is consistent with other studies. Additionally, it reports the highest mean intake of vanadium for the U.S. population to be 18 μg/day. This is in agreement with the EVM, which reports the daily intake of vanadium to be on the order of 10 – 30 μg (EVM, 2002). Typical exposures are therefore likely to be in the range of 250 – 800 fold lower than the UL or 75,000 – 240,000 fold lower than the LOAEL in rats.

The NIEHS bases its nomination on exposure through drinking water and through use as a dietary supplement. While the mean intake of vanadium through drinking water cited by the NIEHS is only 8 μg/day, even the highest value, 140 μg/day, is still significantly lower than the UL. Likewise, the Institute of Medicine reports the average intake of supplemental vanadium at the ninety-ninth percentile to be 20 μg/day (Institute of Medicine, 2001). Weight training athletes are reported to use up to 18 mg of elemental vanadium a day to improve performance; however, it is important to note that it has not been shown to be effective for this purpose. If there is sufficient concern for the toxicity of vanadium to spend millions of taxpayer dollars and thousands of animal lives on new

studies, it would seem that some consideration might be given to limiting the public availability of high-dose preparations as a precaution.

The NIEHS requests chronic toxicity and carcinogenicity as well as multigeneration reproductive toxicity studies. Most of the concern over potential carcinogenicity appears to be based on results from a 2002 National Toxicology Program (NTP) two-year inhalation study of vanadium pentoxide. In this study, the incidence of lung neoplasms increased in male and female mice and, to a lesser degree, in female rats. Notably however, no neoplasms were found in other organs (NTP, 2002). This suggests that the observed effects were the direct result of the inhalation exposure route. The NIEHS notes that administration of tetravalent vanadium compounds has been shown to have impacts on the structures within reproductive organs and that higher dose studies describe decreases in survival rate of weanlings, sperm density and motility, fertility, and litter size. However, the International Programme on Chemical Safety (IPCS) argues that these results do not provide convincing evidence of fertility effects due to significant general toxicity, reflected in decreased body weight gain, observed at the high doses at which they were observed (IPCS, 2001).

The NIEHS summarizes an extensive body of existing data from human studies including short-term and subchronic toxicity studies with both tetravalent and pentavalent vanadium compounds. For example, in the study noted above in which reversible abdominal effects were reported, twelve volunteers were given diammonium vanadotartrate at 75 mg/day for two weeks and then 125 mg/day for the next 5.5 months. In another study, six volunteers were given ammonium vanadyl tartrate at 50-125 mg/day for 45-90 days. No toxic effects were reported in this study. In yet another study, weight-training athletes were given vanadyl sulfate at 0.5 mg/kg/day for 12 weeks and also showed no toxic effects.

In summary, vanadium is poorly absorbed and exhibits generally low toxicity by the oral exposure route. In addition, typical exposures are well below levels what might reasonably cause concern. Finally, there is an existing literature of short-term and subchronic studies in human volunteers. We urge the NTP to assign this nomination a low priority and to rely on additional clinical and retrospective epidemiological studies of exposed populations for any research plan that is developed.

EVM (Expert Group on Vitamins and Minerals) (2002) Review of vanadium. Report No. EVM/00/04.REVISEDAUG2002. Internet address: http://www.food.gov.uk/multimedia/pdfs/evm0004preview.pdf.

Institute of Medicine (2001) Chapter 13: Arsenic, boron, nickel, silicon, and vanadium. In: Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. National Academy Press, Washington, DC, pp. 502-553. Internet address: http://books.nap.edu/openbook.php?record_id=10026&page=502.

IPCS (International Programme on Chemical Safety). 2001. Vanadium pentoxide and other inorganic vanadium compounds. Concise International Chemical Assessment Document 29. World Health Organization, Geneva, Switzerland. Internet address: http://www.who.int/ipcs/publications/cicad/en/cicad29.pdf.

NTP (National Toxicology Program) (2002) NTP technical report on the toxicology and carcinogenesis studies of vanadium pentoxide (CAS No. 1314-62-1) in F344/N rats and B6C3F1 mice (inhalation studies). NTP TR 507. NIH Publication No. 03-4441. Internet address: http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr507.pdf.