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College *	College of Medicine
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Title of Research *	Telomere Dysfunction And Telomerase Reactivation In Human Skin Keratinocytes: A Possible New Mechanism Of PCB Carcinogenesis
Other Authors *	A. Klingelutz, L.W. Robertson, and G. Ludewig
Introduction & Purpose *	Activation of telomerase activity and lengthening of telomeres are key steps in the process of malignant cell transformation. Polychlorinated Biphenyls (PCBs), a group of 209 different congeners, are classified as probable human carcinogens. This study is conducted to explore PCBs effect on telomerase and telomeres and thereby its involvement in carcinogenesis.
Experimental Design *	Immortal human skin keratinocytes (HaCat) were exposed to PCB congeners 28, 52, 126, 153 and Chicago Air Mixture (CAM) at 5µM concentration for 48 days. Medium with compound was changed every 3rd day and every 6th day cells were re-seeded and telomerase activity, telomere length (qPCR), cMyc, hTERT, hTR, CYP1A1 mRNA (RT-PCR), CYP1A1 activity (EROD production), cell cycle distribution (flow cytometry), and superoxide level (DHE oxidation) were determined.
Results *	All PCB congeners reduced telomerase activity and telomere length. PCB126 caused the most prominent reduction of telomerase activity (50%), hTR and hTERT mRNA (10%), telomere length (40%) and cell growth, along with an increase in CYP1A1 mRNA and activity, and in superoxide levels from day 6 to 48; Treatment with PCB126 was continued and from day 54 on, an increase in cell growth, cMyc, hTERT, and hTR mRNA level (to 130%) along with re-activation of telomerase activity (to 100%) and re-elongation of telomere length (to 90%) from day 54 to 90 was observed.
Conclusions *	The increase in cMYC, hTERT, and hTR transcripts after critical telomere shortening may be an indication of genomic instability, a hallmark of carcinogenesis. This study shows for the first time that PCBs initially reduce telomerase activity, telomere length, and cell growth, with possible mechanistic connections to increased CYP1A1 and oxidative stress, but can later lead to telomerase re-activation, telomere lengthening and increased cell growth, all key components in cancer initiation and progression.

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